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THE ROLE OF AN INTRINSIC SPHINCTER MECHANISM IN THE PREVENTION OF REFLUX ESOPHAGITIS

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THE PRESENCE of an intrinsic sphincter mechanism at the lower end of the esophagus is still debated. This study was undertaken to obtain further experimental evidence substantiating the existence of such a mechanism and to ascertain its functional importance. It has been shown by this investigation that the intrinsic mechanism acting alone can maintain normal gastroesophageal competence. These studies further demonstrate that all extrinsic mechanical factors acting together in a normal fashion on an esophageal segment, unprotected by the intrinsic factor, were unable to maintain gastroesophageal competence or prevent esophagitis.

Allison, in his classic article, discussed the physiology of the esophagogastric junction and stated that "although no internal sphincter can be demonstrated, there is an intrinsic mechanism which contributes to competence, for when the esophagus and stomach are removed from the body, a greater pressure is necessary to drive fluid from the stomach to the esophagus than in the opposite direction. If the intrinsic mechanism is ineffective, the diaphragm alone may not be enough to insure complete continence." Nevertheless, he believes that the extrinsic factors are of prime importance.

The previously described extrinsic mechanical factors responsible for the maintenance of esophagogastric competence are: (1) the acute angle of esophageal entry into the stomach, (2) the pinchcock-like action of the crural sling of the diaphragm, (3) the contraction of the oblique muscle fibers of the stomach, and (4) the esophageal mucosal rosette (Fig. 1).

Lerche has brought to our attention the concept of a gastroesophageal segment of expulsion which, he believes, functions as an intrinsic sphincter. This unit is made up of an inferior esophageal sphincter, a saccular area (the vestibule), and the constrictor cardia (Fig. 1).

Recent evidence based on simultaneous pressure recordings and fluoroscopic studies by Fleshler, Hendrix, Kramer, and Ingel-

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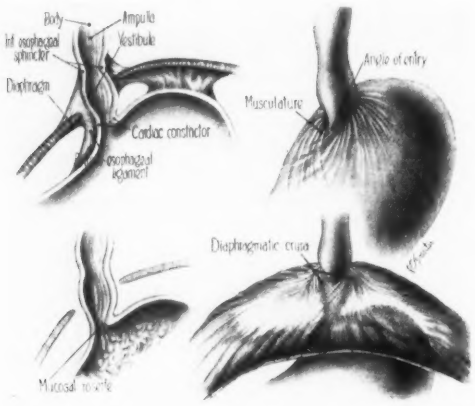


FIG. 1. These diagrams illustrate the extrinsic mechanical factors said to be responsible for maintaining esophagogastric competence. Also shown is the area designated "vestibule" and described by Lerche as the site of intrinsic sphincteric action.

finger and Schlegel and Code supports the concept of an intrinsic esophageal sphincter mechanism at the lower end of the esophagus. A high resting pressure has been demonstrated in the lower esophageal area where changes can be initiated by swallowing. Meiss, Grindlay, and Ellis have shown in dogs that removal of the esophagogastric junction always resulted in esophagitis. In their experiments this esophagitis was not prevented when the newly created esophagogastric anastomosis was brought below the diaphragm, when the esophagus was narrowed or when an acute angle was created between the esophagus and the stomach. They concluded that a physiologic intrinsic sphincter mechanism must be present.

Lyons, Ellis, and Olsen commented that "over the years, the weight of medical evidence and opinion has favored the presence of a sphincter at the cardia, intrinsic to the gullet. For practical purposes the presence of such a sphincter may be considered established. The question which remains is whether this sphincter alone can be responsible for complete competence. Clinical and experimental evidence suggest that it cannot." Our experimental study indicates that the intrinsic sphincter mechanism *does* act to maintain complete esophagogastric competence in the dog.

Friesen and Miller have shown in dogs that the esophagogastric junction remains competent when deprived of its mechanical factors. They made a pouch of the junctional segment by transecting the esophagus 3 centimeters above the diaphragm. This pouch, in some cases rendered achalasic by depriving it of its vagal innervation, was left either in its normal position in the hiatal canal or was placed within the abdomen. The esophagogastric anastomosis was located within the dome of the diaphragm. In the mucosa within the isolated pouch inflammation did not develop and presumably regurgitation did not occur. However, this method has the disadvantage of (1) retaining mechanical support while subjecting the pouch to negative thoracic pressure or (2) when deprived of its mechanical support, exposing the pouch to positive intra-abdominal pressure which might in itself prevent gastric reflux. Therefore, we have designed the following experimental procedure.

METHOD

Experiments were carried out on 25 healthy mongrel dogs under intravenous

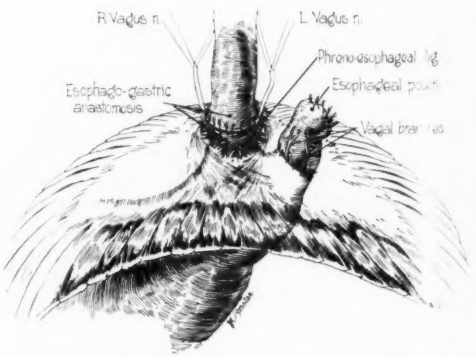


FIG. 2. This drawing represents the isolation of the lower 3 to 4 centimeters of the esophagus (vestibular area) as a supradiaphragmatic pouch through the tendinous portion of the diaphragm. Note the new esophagogastric junction within the hiatal canal. The cut left leaf of the phrenoesophageal ligament has been resutured.

nembutal anesthesia using a positive pressure respirator. Four separate control situations were utilized.

In 14 dogs, a left thoracotomy was performed, and the lower 3 to 4 centimeters of the esophagus were dissected free with careful isolation of the right and left vagi and preservation of all visible vagal fibers. The distal 3 centimeters of the esophagus (vestibular area) were converted into a pouch and brought through the tendinous portion of the diaphragm after the left lateral leaf of the phrenoesophageal ligament had been incised. Aside from this, the hiatal canal was not disturbed (Fig. 2). Thus the lower esophageal segment was deprived of all previous mechanical support contributing to its competence but retained its vagal innervation and was exposed to the negative intrathoracic pressure.

Control 1. Next, in these 14 animals, the proximal cut end of the esophagus was anastomosed to the cardia of the stomach through the hiatal canal and the previously cut left phrenoesophageal ligament sutured to the new anastomotic site (Fig. 2). This newly created esophagogastric junction possessed all of the mechanical factors of competence but was deprived of the area thought to contain an intrinsic sphincter. Thus, a situation was established in which the extrinsic mechanical factors alone were present at the new esophagogastric junction while, in the same animal, an isolated lower esophageal segment was protected only by intrinsic neuromuscular factors.

Control 2. In 3 dogs the same operation was performed as in the first 14 animals but with the lower esophageal pouches inverted into the gastric lumen to determine whether normal gastric contents acting on an unprotected lower esophageal segment would produce esophagitis. This experimental procedure was first performed by Friesen (Fig. 3c).

Control 3. In 4 animals, a pouch was constructed by transecting the esophagus between its middle and lower one-third and anastomosing the distal cut end to the cardia

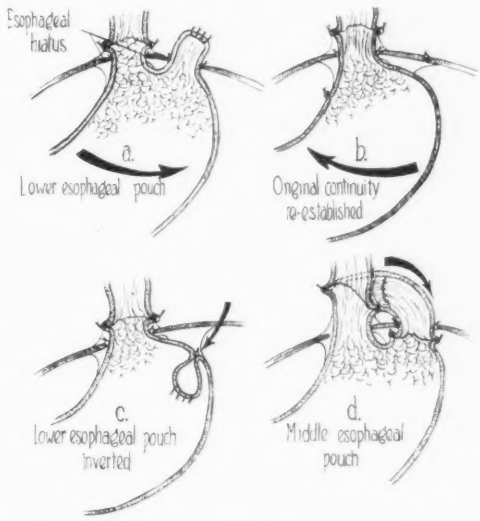


FIG. 3. a, The isolated lower esophageal (vestibular) pouch. b, The restoration of the intact pouch to its original position when esophagitis developed in the esophagus above the esophagogastrostomy (Control 4). c, The inversion of the lower esophageal segment into the gastric lumen (Control 2). d, The middle esophageal supradiaphragmatic pouch (Control 3).

through the tendinous portion of the diaphragm. An esophagotomy was performed in the anterior wall of the rotated distal esophageal segment. The proximal cut end of the esophagus was then anastomosed to the proximal lip of the esophagotomy to establish esophageal luminal continuity. A pouch was created by suturing the distal lip of the esophagotomy to the posterior wall just distal to the anastomosis, with careful preservation of all vagal fibers (Figs. 3d and 4).

Control 4. Four animals were treated initially in the same manner as the first 14 dogs. When esophagitis developed at the reconstructed esophagogastric junction and the mucosa of the pouch remained intact, a second operation was performed to restore the original anatomy by taking down the esophagogastric anastomosis and returning the pouch to its normal position as the lower esophageal segment. If the esophagitis should clear, this would be conclusive evidence that the intrinsic sphincter was the most impor-

TABLE I.—SUPRADIAPHRAGMATIC VESTIBULAR POUCHES WITH CONTROL 1

Dog No. Date of operation	*Gastric analysis, free HCl*	*Condition of junction**			
		Esophagoscopy	*Autopsy or reoperation*	*Condition of pouch*	*Disposition*
264 9-18-57	45 units	2 mos. postop., mild esophagitis	Mild esophagitis	Intact	Sacrificed, 15 weeks
281 10-4-57	65 units	Not done	Erosion, mild esophagitis	Intact	Died, 17 days
311 11-8-57	No free acid	7 days postop., moderate esophagitis	Ulceration	Intact	Died, 7 weeks
315 11-19-57	No free acid	6 days postop., moderate esophagitis	Superficial erosion	Intact	Sacrificed, 4 weeks
319 11-20-57	55 units	21 days postop., severe ulceration	Severe ulceration	Intact	Died, 5 weeks
325 11-22-57	30 units	19 days postop., moderate esophagitis	Moderate ulceration	Intact	Died, 8 weeks
330 11-26-57	55 units	Not done	Hemorrhagic ulcerative esophagitis	Intact	Sacrificed, 6 weeks
333 12-3-57	70 units	20 days postop., moderate esophagitis	Moderate esophagitis	Intact	Died, 5 weeks
335 12-4-57	20 units	16 days postop., moderate esophagitis	Severe esophagitis with ulceration	Intact	Died, 4 weeks
342 12-6-57	45 units	8 days postop., mild esophagitis	Mild erosion	Intact	Died, 16 days
416 1-28-58	60 units	2 weeks, mild esophagitis; 6 weeks, mild esophagitis; 12 weeks, moderate esophagitis	4 mos., re-exploration	Reoperation 4 mos. postop., pouch intact, actively contracting	Alive, 15 mos.
466 2-18-58	55 units	3 weeks, moderate esophagitis; 8 weeks, mild esophagitis; 9 mos., moderate esophagitis			Alive, 14 mos.
485 3-6-58	55 units	1 week, no esophagitis; 3 mos., no esophagitis; 6 mos., marked esophagitis	7 mos., sacrificed, marked esophagitis	Intact	Sacrificed, 7 months
551 5-1-58	43 units	4 mos., marked esophagitis	5 mos., sacrificed, marked esophagitis, gastric mucosal extension into esophagus	Intact	Sacrificed, 5 months

*Esophagus above the esophagogastrostomy.

TABLE II.—INVERTED POUCH, CONTROL 2

Dog No. Date of operation	*Gastric analysis, free HCl*	*Condition of junction* at autopsy or reoperation*	*Condition of pouch (vestibular)*	*Disposition*
343 12-6-57	40 units	Mild esophagitis	Inverted severe esophagitis	Sacrificed, 3 weeks
358 12-14-57	No free acid	Mild esophagitis	Inverted severe esophagitis	Died, 2 weeks
366 12-18-57	30 units	Mild erosion	Inverted severe esophagitis	Sacrificed, 20 days

*Esophagus above esophagogastrostomy.

tant factor in maintaining gastroesophageal competence (Fig. 3a and b).

Postoperatively, all dogs were maintained on liquids for 2 days and then were placed on a regular kennel diet. Penicillin was given twice a week for 2 weeks. Esophagoscopy was performed 1 or more times during the postoperative period, and gastric analysis was done to confirm intact vagal innervation. The animals that survived were either sacrificed or reoperated upon, and microscopic sections were made from the anastomotic sites and pouches to confirm the findings noted by direct observation.

RESULTS

Table I shows the results obtained from 14 dogs in which the lower esophageal seg-

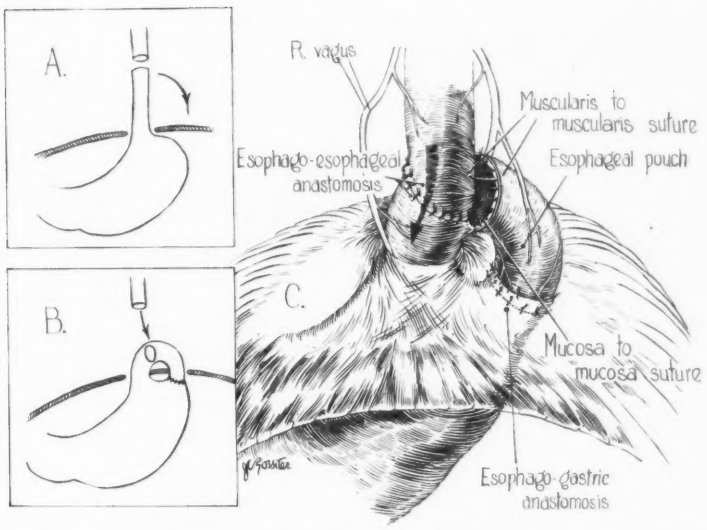


FIG. 4. A and B, The method of creation of a supradiaphragmatic middle esophageal pouch. C, The esophagoesophagostomy providing esophageal continuity and the middle esophageal pouch. The approximation of muscularis to muscularis between the esophagus and esophageal pouch is not shown.

ment of the esophagus was transposed as a supradiaphragmatic pouch and a new esophagogastrostomy created through the hiatal canal. These animals were observed for from 16 days to 15 months. The mucosa of the transposed pouch was always free of inflammatory changes. However, the changes in the esophagus above the newly created esophagogastric junction varied from mild inflammation and superficial erosion to severe ulceration (Fig. 5). These esophageal findings were initially observed through the esophagoscope and confirmed by biopsy and later studied in the autopsy specimen. Esophagoscopy demonstrated that the development of esophagitis differed in the time of appearance and degree of severity; but it always occurred above the esophagogastric junction when the intrinsic sphincter mechanism was absent, even though all the protective extrinsic mechanical factors were intact.

Dog 416 was reoperated upon 4 months after the initial operation. The supradiaphragmatic pouch was actively contracting while the remainder of the esophagus remained inactive. This animal was saved for further investigations regarding the motility and pressure changes within the transposed pouch.

In Table II, the results obtained after inverting the lower esophageal (vestibular) segment into the gastric lumen are summarized. In all 3 of these pouches, marked inflammation developed which demonstrates that esophagitis was invariably present when the lower esophageal mucosa was exposed to gastric secretions without sphincteric protection (Fig. 6).

Table III represents the changes which resulted when a portion of the esophagus, other than the terminal segment, was transformed into an innervated pouch located above the diaphragm in a negative pressure area. This was comparable to the position of the transposed terminal segmental pouch described in Table I (Fig. 4). These animals were followed up for from 3 weeks to 5 months, and in all pouches extensive or ulcerative esophagitis developed. The nor-

TABLE III.—SUPRADIAPHRAGMATIC MIDDLE ESOPHAGEAL POUCH, CONTROL 3*

Dog No. *Date of operation*	*Gastric analysis, free acid*	*Condition of junction at autopsy*	*Disposition*	*Autopsy, middle esophageal pouch*
490 3-13-58	55 units	No esophagitis	Sacrificed 3 weeks postop.	Ulcerative esophagitis
499 3-21-58	38 units	No esophagitis	Sacrificed 5 mos. postop.	Ulcerative esophagitis
539 4-23-58	40 units	No esophagitis	Sacrificed 4 mos. postop.	Marked esophagitis
567 5-13-58	48 units	No esophagitis	Sacrificed 4 mos. postop.	Marked esophagitis

*Esophagoscopy not performed since junction was not disturbed.

TABLE IV.—INITIAL VESTIBULAR POUCH, REANASTOMOSIS, REVERSAL ESOPHAGITIS, CONTROL 4

Dog No. *Date of initial operation*	*Gastric analysis, free HCl*	*Condition of junction*			*Condition of pouch at reoperation*	*Disposition*	*Autopsy findings*
		Esophagoscopy	*Reoperation and reanastomosis*	*Esophagoscopy, postreanastomosis*			
322 11-21-57	40 units	3 wks. after initial operation moderate esophagitis	8 wks. after initial operation moderate esophagitis	7 days, esophagitis mild; 6 wks., no esophagitis; 10 wks. no esophagitis; 18 wks. no esophagitis	Intact	Sacrificed 10 mos. after initial procedure; 8 mos. after reoperation	No esophagitis
338 12-5-57	65 units	4 wks. after initial operation moderate esophagitis	9 wks. after initial operation, moderate esophagitis	5 wks., no esophagitis; 9 wks., no esophagitis; 17 wks. no esophagitis	Intact	Sacrificed 9 mos. after initial procedure; 7 mos. after reanastomosis	No esophagitis
463 2-18-58	65 units	1 mon. after initial operation no esophagitis; 2 mos., moderate esophagitis	4 mos. after initial operation; moderate esophagitis	1 mon., no esophagitis	Intact	Sacrificed 6 mos. after original procedure; 2 mos. after reanastomosis	No esophagitis
479 2-27-59	Not done	3 wks. after initial operation ulcerative esophagitis	4 wks. after initial operation, marked esophagitis	10 days, resolving esophagitis; 27 days no esophagitis	Intact	Sacrificed 2 mos. after initial procedure; 30 days after reanastomosis	No esophagitis

mal junctional segment was undisturbed and no esophagitis developed in this area (Fig. 7).

Table IV represents the changes in 4 dogs treated initially in the same manner as the original group of 14 animals. The mucosa of all these pouches was free of inflammation (as in the original group) and in all moderate or marked esophagitis developed in the esophagi above the newly created esophagogastric junctions. A second operation was performed, and the intact pouch was restored to its normal anatomic position after taking down the esophagogastric anastomosis (Fig. 3a and b). Esophagoscopy demonstrated complete resolution of the esophagitis between the fourth and sixth week. It was most interesting to observe the gradual resolution of this inflammatory process. Animals were sacrificed from 1 to 8 months after reanastomosis and, in all cases, the esophagitis had completely disappeared. A biopsy from the esophagus at the time of the reanastomosis shows the characteristic inflammatory reaction present (Fig. 8a). At autopsy, the anatomically restored esophagus in this same animal showed complete resolution of the infiltrating process as evidenced by the glistening, normal mucosa shown in Figure 8b. Microscopic sections confirmed the gross appearance (Fig. 8c).

DISCUSSION

The determination of the exact location of the mechanism responsible for preventing

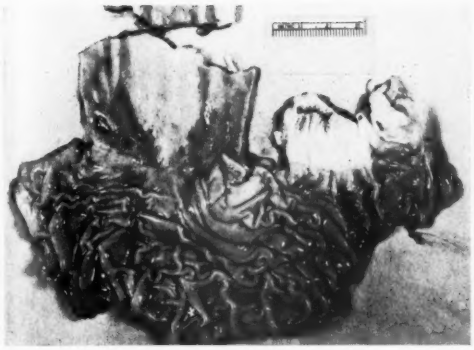


FIG. 5.

FIG. 6.

FIG. 5. An autopsy specimen from dog 319 showing ulcerative esophagitis above the newly created esophagogastric anastomosis on the left and the normal mucosa of the supradiaphragmatic lower esophageal (vestibular) pouch on the right. A small segment of the upper one-third of the esophagus is shown in the upper left-hand corner to illustrate the extent of the process in this animal.

FIG. 6. An autopsy specimen of the inverted esophageal pouch (Control 2). Note the inflamed appearance of the mucosa of the inverted pouch.

FIG. 7. (Compare with Fig. 4.) This is an autopsy specimen of a middle esophageal supradiaphragmatic pouch from dog 567 (Control 3). An ulcer can be seen in the opened pouch and illustrates inflammation developing in a supradiaphragmatic esophageal pouch unprotected by an intrinsic sphincter mechanism. The anastomotic site of the esophagoesophagostomy can be seen (*a*). This area is normal. Note the superior limits of the pouch (*b*).

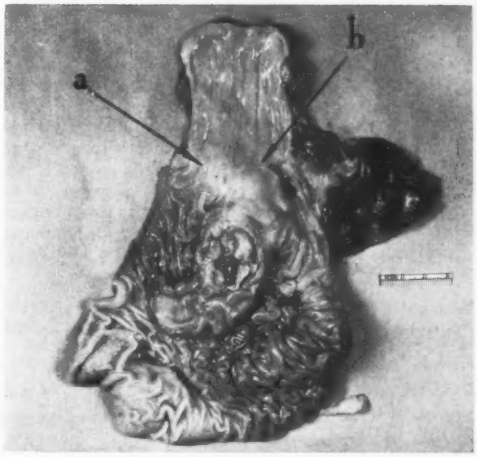
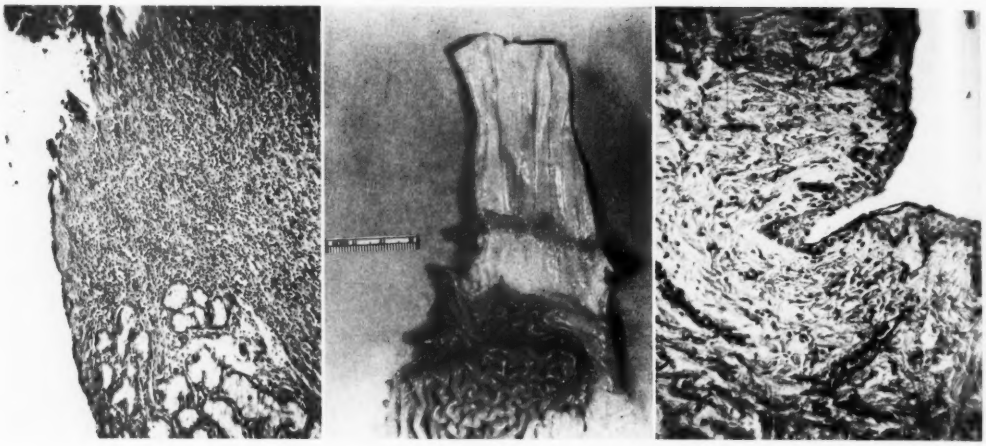


FIG. 7.

esophageal reflux is most important for the successful management of benign and malignant conditions which involve the esophagogastric junction. This experimental study demonstrates an anatomic location in the lower esophagus where a mechanism exists which maintains esophagogastric competence. Further study is necessary to determine the exact nature of this mechanism. Motility and pressure studies offer a path for investigation.

To date, no completely satisfactory method of reconstruction of the esophagogastric area has been found, although the results of jejunal interposition as developed by Merendino have shown promise. The peristalsis of the jejunum may act to prevent exposure of the esophagus above to prolonged contact with gastric juices. Colon interposition is also being utilized. The Heller procedure used in the surgical treatment of achalasia apparently divides the area occupied by the intrinsic sphincter. The length of this vertical muscular esophagogastric incision varies in different clinics and standardization of the operative procedure is necessary before an accurate over-all clinical evaluation can be made. Postoperative results have been good in a number of these cases but esophagitis may follow this procedure. This fact offers evidence toward the concept of a motile segment rather than a true sphincter mecha-



a b c

FIG. 8. a, This photomicrograph was made from a biopsy at esophagoscopy in dog 338. The lower esophageal segment was isolated and an esophagogastrostomy created with all extrinsic mechanical factors acting on the anastomosis. Marked inflammatory changes are seen in this area above the esophagogastrostomy. b, Autopsy specimen from the same animal with the pouch returned to its normal position. A rim of gastric mucosa is present between the restored pouch and the esophagus. Note the reversal to a normal glistening mucosa in the area above the restored lower esophageal segment. c, A section of the esophagus from the autopsy specimen. The mucosa is now free of inflammatory infiltrate (compare with Fig. 8a).

nism since cutting across a sphincter should destroy its function. A motile segment would still retain expulsive activity. The interposition of the pyloric sphincter with pedicled artery and nerve, as performed experimentally by McGannon in dogs, has been successful and represents the first attempt to restore intrinsic sphincteric control. The operation employed by Ellis which entails resection of the area of esophageal involvement, bilateral vagotomy, excision of the distal stomach including the antrum, with the re-establishment of intestinal continuity has proved promising in his hands. However, this is a most formidable surgical procedure.

The initiating factor in the development of a sliding hiatal hernia may be an alteration of the intrinsic sphincter mechanism which results in esophageal reflux with spasm followed by contracture and shortening of the esophagus. If this assumption is true, the logical therapeutic approach would be to restore an intrinsic sphincter mechanism, because extrinsic mechanical factors alone would not prevent recurrence.

The contraction rate of the terminal esophageal segment in normal dogs and in animals with various reconstructive procedures which replace the terminal segment may further clarify the activity present. We have devised a technique in which the normal esophagogastric junction is removed and a segment of diaphragm with its phrenic innervation intact is transplanted between the muscularis of the esophagus and stomach to determine if a transplanted neuromuscular segment will serve as an intrinsic sphincter. The findings of this study will be reported in detail elsewhere. Our primary objective is to develop a simple operative procedure that will restore competence following removal of the lower esophageal segment.

SUMMARY

This experimental laboratory study was performed in an effort to isolate the mecha-

nism responsible for the prevention of esophageal reflux. Inflammatory changes never developed in the lower esophageal (vestibular) segment with its vagal innervation intact, when isolated from all extrinsic mechanical factors in a negative pressure area. Four control situations were utilized: (1) All the extrinsic mechanical factors were allowed to act on an esophagogastric anastomosis after removal of the normal vestibular segment. (2) Vestibular segments were permanently inverted into the gastric lumen. (3) A middle esophageal pouch was constructed within a negative pressure area with its vagal innervation intact. (4) The isolated intact lower esophageal pouch, when returned to its usual anatomic position, was able to reverse the inflammatory process which had developed at the site of the esophagogastrostomy.

CONCLUSIONS

1. An intrinsic "sphincter" mechanism at the lower end of the esophagus was demonstrated which alone maintained normal esophagogastric competence and prevented esophagitis when vagal innervation was preserved.

2. The midportion of the esophagus did not display such an intrinsic protective mechanism, and esophagitis developed when this segment was isolated as a supradiaphragmatic pouch with its vagal innervation preserved.

3. The extrinsic mechanical factors acting together on an esophageal segment other than the intrinsically protected vestibular area did not maintain gastroesophageal competence or prevent esophagitis.

4. The esophageal inflammation which developed proximal to the esophagogastrostomy after the normal lower esophageal segment was transplanted and isolated showed a complete regression with the return of a normal mucosa when this segment was restored to its normal anatomic position.

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RADIOIODINE IN THE EVALUATION OF THE THYROID NODULE

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THE USE of radioiodine localization studies in the diagnosis of thyroid disease is based upon the inability of certain abnormalities such as hemorrhagic goiter, thyroiditis, and most carcinomas and adenomas to concentrate iodine. Such localization studies have gained impetus with the availability of an automatic scanning counter to record the topographic distribution of the radioactive material. The record thus obtained has been referred to as a scintigram. In a previous publication (3), it was indicated that the delineation of nonconcentrating areas of the thyroid gland by this instrument was limited to those lesions greater than 1½ centimeters in diameter. Certain modifications in radiation counters have been developed by Francis and associates to increase the sensitivity for small nonconcentrating areas of tissue. Studies with the newer type counting system have been carried out in our laboratory using plastic models of the thyroid gland filled with radioiodine. In addition, the variations in radioiodine concentration, as perceived by the scintillation counter moving back and forth over the thyroid area, were recorded by means of a conventional counting rate meter and a strip-chart recorder. From these data, three-dimensional models of isotope distribution were constructed.

METHODS

The most important problem in thyroid localization studies results from an interaction of gamma radiation with tissue at a distance from the thyroid gland and its reflection into the counter aperture. For example, under conditions usually employed for the thyroidal radioiodine uptake procedure, the counting rate of a vial of radioiodine placed over the neck of a human subject is about 20 per cent greater than if the same source were counted in air. Since the reflected or scattered radiation undergoes some loss in energy as a result of the direction-changing collision, it is possible by using the stable electronic circuit in a single channel pulse height analyzer to discriminate against all radiation not directly emanating from the source. This fact is well illustrated in Figure 1. In the left half (Fig. 1a) is a scintigram of a 50 milliliter volumetric flask containing radioiodine and obtained by using conventional counting equipment. In contrast, the scintigram in the right half of the illustration (Fig. 1b) was made by using the backscatter discriminator circuit. The result was a more accurate outline of the radioisotope distribution.

Another innovation is the use of a "focusing-type" lead shield. The lead shielding on the counter of conventional scanning equipment has only a single small aperture, and radiation striking the surface of the detector crystal can come only from a small area of tissue. In the newer counting system, the shield is a tapered lead block in which 19 hexagonal holes have been drilled in a conical fashion. The axis of these holes meet at a point 2 inches from the face of the shield. When the counter is positioned approximately 2 inches from tissue containing a gamma emitting radioisotope, radiation coming from a very small area will strike the detector crystal in 19 places, corresponding to the holes in the lead shield. The result is a considerable increase in counting efficiency.

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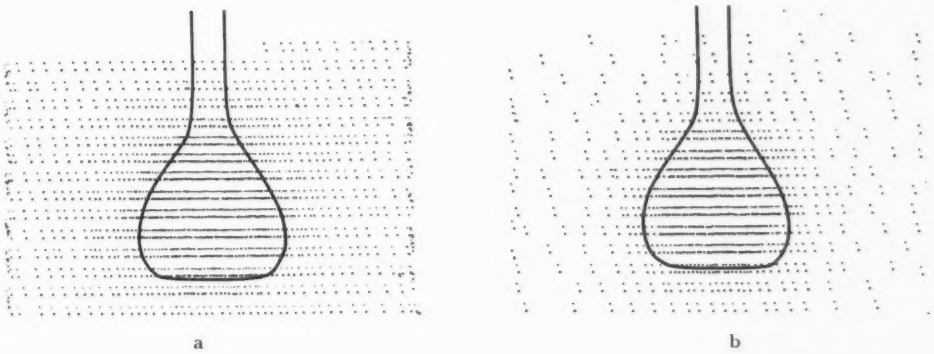

a b

FIG. 1. Scintigrams of a 50 milliliter volumetric flask containing radioiodine. a, Note the tendency in this scintigram for the marks to exceed the actual outline of the flask. b, This tracing was obtained by using the pulse height discriminator circuit.

Our studies were made with plastic thyroid models which were constructed by the plastic eye clinic of this hospital. Various types of defects were introduced into these models. They were then filled with a solution of radioiodine of appropriate concentration prior to scanning. The actual scan was done with the plastic model mounted on a lucite block so that the usual conditions of scatter in the neck could be simulated.

The counter system was adjusted in each individual determination to obtain the greatest possible contrast between the background and the radioactivity in the thyroid model. The output of the scaling circuit of the scanner was also connected to a counting rate meter and its graphic recorder. In this way, any variation in radioiodine concentration perceived by the counter on each traverse across the model is indicated both on the ordinary scintigram record and as a parabolic curve on the counting rate record. Three-dimensional models were constructed from each scintigram by transferring the counting rate meter record to cardboard, trimming the outline, and mounting them in slotted wooden blocks.

RESULTS

A number of experiments were performed to test the counter's ability to detect deep-lying nonradioactive areas in a radioiodine solution. It was found that when various sized beakers were filled with radioactive iodine, the ability of the counter to detect displacement of the radioactive solution by an empty 50 milliliter volumetric flask was poor, or nonexistent in most instances. The usefulness of this particular counter shield, therefore, is limited to localization studies in the thyroid gland or similar shallow areas. Since the counting rate could be controlled somewhat by adjustments of the electronic circuits, a variety of concentrations of radioiodine were introduced into the plastic thyroid gland models in order to determine the optimum combinations of radioisotope concentration and counter system setting. Experimentally, it was found that quantities of radioactive iodine ranging between 50 and 150 microcuries could be counted with ease.

A series of scintigrams was performed of thyroid models containing defects of variable size. The large defects were quite obvious on the scintigram as a relative decrease in the concentration of the radioactivity manifested by greater space in between the marks. This is equally true of an older model scintiscanner record as demonstrated in Figure 2. In the upper left-hand corner of the illustration is a scintigram obtained with our new counting system. In the

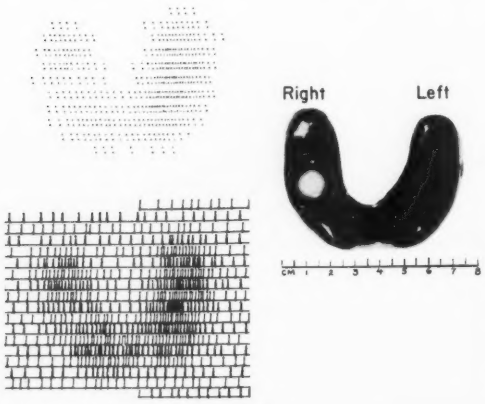

FIG. 2

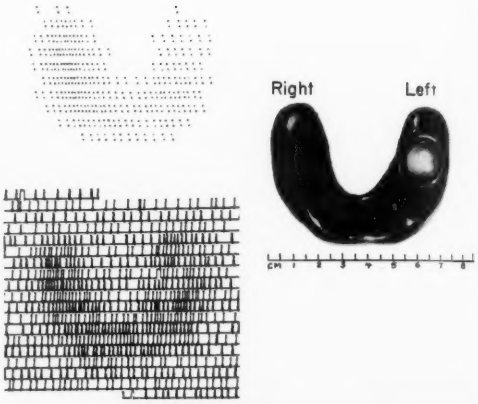

FIG. 4

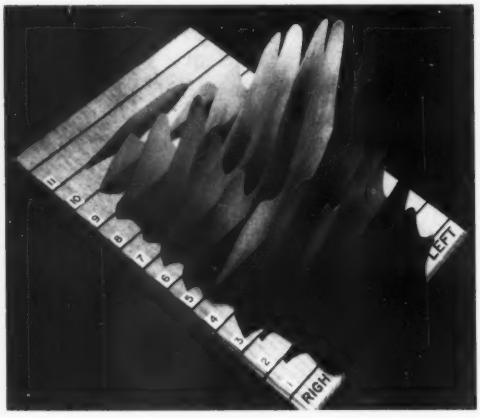

FIG. 3

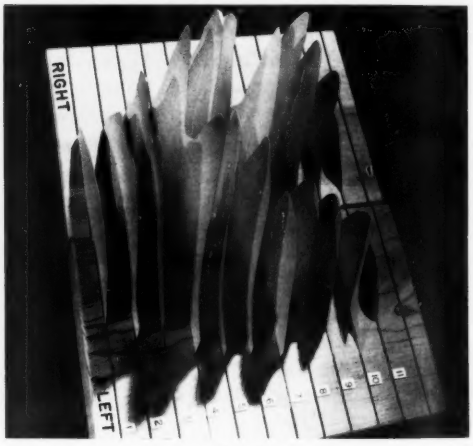

FIG. 5

FIG. 2. A radioiodine filled plastic thyroid model accompanied by a pair of scintigrams obtained with it. The upper scan was made by using the modified counter; the lower scan with a conventional counter system.

FIG. 3. An isometric model of the radioiodine distribution in the plastic thyroid model depicted in Figure 2. The decreased counting rate on the right corresponds to the defect in the right lobe of the plastic thyroid model.

FIG. 4. A plastic thyroid model and its accompanying scintigram as in Figure 2. Here the defect is 1½ centimeters in diameter.

FIG. 5. Isometric model of the radioiodine distribution in the plastic model in Figure 4. The decreased concentration is apparent in lines 7 through 10.

lower left-hand corner is depicted the scintigram obtained with a conventional scanner. To the right is seen the actual plastic thyroid model indicating an oval defect of approximately 2 centimeters in diameter. In both instances, the defect is demonstrated by a relative decrease in counting rate over the involved area. In Figure 3 is presented a three-dimensional model of the distribution of radioactivity developed in the performance of the scintigram of the plastic model in Figure 2. The difference in the relative heights of the two sides of the model is apparent from line 3 through line 7. Figure 4 represents the scintigrams obtained of a plastic thyroid model with a defect of ap-

proximately 1½ centimeters in diameter. Again, the defect is demonstrated as a relative decrease in counting rate over the involved area. Although apparent in both scintigrams, the defect in this plastic thyroid is less obvious than the one in Figure 2. Nevertheless, the three-dimensional model depicted in Figure 5 quite definitely shows a decrease in counting rate in lines 7 through 10. In Figure 6 is the three-dimensional model of a plastic thyroid gland containing a defect approximately 0.7 centimeter in diameter. This defect could not be appreciated on the scintigram obtained from either of the scanning machines. Nevertheless, it is present in the three-dimensional model appearing as a difference in the counting rate over the right and left thyroid lobes as is demonstrated in lines 7, 8, and 9.

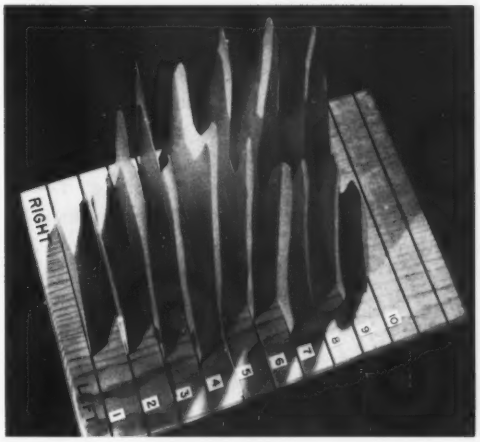

FIG. 6. The counting record of a plastic thyroid model with a left lobe defect 0.7 centimeter in diameter. The defect is apparent in lines 7, 8, and 9. It was not evident on either of the scintigrams.

DISCUSSION

The use of differential counting in the detection of the presence of a potentially malignant thyroid lesion is well established. According to Johnson and Perlmutter and their associates, of those nodules found to have an inability to concentrate radioactive iodine, 20 to 30 per cent will be malignant. In a previous study (3), the ability of the conventional scanning counter to detect a small radioiodine poor area in the thyroid has been questioned. A more recent approach to the scanning procedure has been the use of a single channel pulse height analyzer and a focusing lead shield for greater efficiency in counting. An investigation was made of the ability of this counting system to detect abnormalities in the plastic thyroid models as compared to a conventional scintiscanner with a single aperture collimator. In the few instances of dual study reported here, the modified counter did not add materially to the diagnostic accuracy as reflected by the scintigram. On the other hand, the recording of the radioiodine distribution as indicated in the three-dimensional cardboard cutouts was a more consistent and reliable method for studying thyroid gland abnormalities. Defects in the scanning pattern were perceived on the three-dimensional models even when they were not obvious on the scintigram. The result of our clinical studies up to the present time would lead us to a similar conclusion.

The detection of a defect in radioisotope distribution on the scintigram depends upon the ability of the eye to estimate concentration from the spacing of the marks. Subtle changes can be readily overlooked. Nevertheless, gross changes in concentration are apparent on the scintigram when the lesion is large. Because of our long familiarity in the use of the scintigram for interpretation, we intend to continue to employ this method. However, as time goes by, we expect to lean more heavily on the record obtained from the counting rate meter record and the three-dimensional model of isotope distribution which may be constructed from it.

SUMMARY

1. A study has been made of certain refinements in radiation counter design as an indicator of abnormalities of thyroidal radioiodine distribution pattern in the scintigram. These studies were carried out with

plastic thyroid models containing a variety of radioiodine poor defects.

2. Little improvement was noted in the ability of this modified counting system to perceive small areas of poor radioiodine concentration.

3. Three-dimensional models of radioiodine concentration were much more accurate in detecting abnormalities in the radioiodine distribution than was simple inspection of the scintigram.

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A CLINICAL STUDY OF 25 PATIENTS WITH CARCINOID TUMORS OF THE RECTUM

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IN RECENT YEARS, considerable attention has been given to carcinoid tumors of the gastrointestinal tract, partially because of the difficulties associated with predicting their malignant potential, and partially as a result of the peculiar syndrome occasionally found to accompany carcinoids which have metastasized. It is only within the last decade, however, that reports of carcinoid tumors of the rectum have appeared with any frequency and to date 225 case descriptions have been recorded.

Despite the sizable number of case reports, there exists much uncertainty regarding the behavior and management of the rectal carcinoid. This may be attributed to the fact that no one surgeon or clinic has reported wide experience with this lesion. The largest series recorded is that of Jackman, which does not include detailed follow-up. In the hope of acquiring additional knowledge regarding the nature and curability of this lesion, we have examined the records of 25 cases of carcinoid of the rectum treated at the Hospital of the University of Pennsylvania during the 25 year period starting in 1933, and wish to report the results of our analysis.

HISTORY

Although Langhans probably first reported a gastrointestinal carcinoid in 1867, Lubarsch provided the first detailed description of this lesion in 1888 when he reported a case of multiple small submucosal tumors of the ileum. In 1890 Ransom reported a carcinoid tumor of the ileum with metastases. Nevertheless, 17 years later Oberndorfer suggested the term "carcinoid" because he believed this neoplasm to be benign despite its resemblance to adenocarcinoma. Gosset and Masson in 1914 produced histologic evidence that the carcinoid tumor develops from the Kulchitsky or argentaffin cell.

In 1912 Saltykow reported the first case of carcinoid of the rectum. The initial publication in the American literature was that of Brunschwig in 1933. As late as 1942, Stout could find only 6 cases of rectal carcinoid in the entire medical literature. Since that time, wider recognition of this tumor combined with increased use of periodic sigmoidoscopy as a routine diagnostic procedure has served to expand the volume of writing considerably.

In 1952, Erspamer and Asero showed that the mother cell of the carcinoid tumor, the Kulchitsky cell, secretes a physiologically potent substance called serotonin or 5-hydroxytryptamine. Although in 1930, Cassidy reported a case of pulmonary valvular stenosis associated with a malignant carcinoid which had metastasized, he failed to distinguish any relationship between the two lesions and it was not until 1952 that recognition was given to a group of functional symptoms associated with malignant carcinoids which had spread to the liver. Shortly after there appeared the independent reports of 3 groups of investigators—Thorson and his associates in Sweden, Isler and Hedinger in Switzerland, and Rosenbaum and his associates in the United States—describing the malignant carcinoid syndrome. In the same

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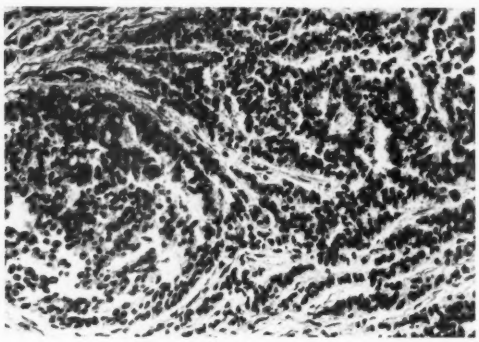

FIG. 1. Photomicrograph of a rectal carcinoid tumor showing nests of small, uniform polygonal epithelial cells lying in a fibrous stroma. ×146.

year, Lembeck attributed these peculiar clinical phenomena to excessive production of serotonin when he isolated this material from a malignant carcinoid.

PATHOGENESIS

Forbus, in 1925, provided an excellent account of the many theoretic explanations of carcinoid histogenesis. These included origin from pancreatic rests, from remnants of the omphalomesenteric duct, from heterotopic embryonic material, and from Auerbach's plexus. Carcinoids have been likened by some authors to basal cell cancer of the skin, to nevi, and to endothelial sarcoma. Despite these varied hypotheses, the original proposal of Lubarsch that these lesions originate in cells of the crypts of Lieberkühn has been generally accepted. More specifically, evidence strongly indicates that carcinoids arise from the Kulchitsky cells of the crypts.

In 1910 Huebschmann suggested that either the Paneth cell or the Kulchitsky cell was the source of origin of the carcinoid tumor. However, it remained for Gosset and Masson in 1914 to demonstrate that both the cells of the neoplasm and the normal Kulchitsky cell contain cytoplasmic granules which stain deeply when treated with ammoniacal silver nitrate. Accordingly, Masson applied the name "argentaffine" to these cells and subsequently the tumor was given another of its many titles, argentaffinoma. Recently, Pearse has demonstrated by histochemical means that the granules of carcinoid tumors are identical with those of Kulchitsky cells, thereby adding credence to Masson's work.

In man, Kulchitsky cells occur in the epithelium of the gastrointestinal tract from the gastric cardia to the anus, as well as in the biliary tree and in the lining of the major pancreatic ducts. They are particularly common in the crypts of Lieberkühn and are most concentrated in the appendix. No carcinoid tumor has ever been found to originate in an area devoid of Kulchitsky cells.

PATHOLOGY

Gross. Extra-appendiceal carcinoid tumors characteristically appear as one or more firm, yellow or gray, submucosal nodules, but occasionally they are polypoid, ulcerating or annular and constricting. The overlying epithelium is usually intact with the neoplasm movable beneath it. Occasionally the mucosa covering a large rectal lesion is eroded by solid fecal matter, and the ulceration results in an appearance not unlike that of adenocarcinoma. Of the 10 rectal lesions in our series which were larger than 2 centimeters in diameter 3 were ulcerated, while none of the smaller tumors developed mucosal erosion.

Microscopic. Microscopically, these tumors consist of nests, columns, or masses of small, uniform, round or polygonal epithelial cells lying in a fibrous stroma (Fig. 1). Continuity between the epithelium of the overlying crypts and the tumor mass has been demonstrated. The clumps of tumor cells are usually solid without evidence of degeneration. The prominent nuclei are most often round with a well defined nuclear membrane and abundant finely stippled chromatin which is deeply basophilic. The cytoplasm is pale, indistinct, and acidophilic containing numerous acidophilic granules. The tumor cells are sometimes grouped around a space in such a manner as to simulate gland or rosette formation with the central space often containing an amorphous acidophilic material.

Stout has illustrated the "ribbon-like festoon" of tumor cells seen most often in rectal carcinoids. A single tumor may show more than one architectural pattern. The fibrous or hyaline connective tissue stroma is variable in amount but is commonly prominent. A pseudocapsule is often formed by condensation of smooth muscle fibers at the periphery of the tumor. Mitoses are rare. However, pleomorphic tumors do occur with anaplastic cells, multinucleated cells, gigantic and bizarre nuclei, and frequent mitoses. These anaplastic forms do not necessarily metastasize.

The granules often present in the cells of carcinoid tumors are likely artefacts produced by formal fixation. Unstained, the granules are yellow and react with many staining agents including iron hematoxylin, eosin, acid fuchsin, Schmorl's ferric-ferricyanide, ammoniacal silver nitrate, ultraviolet light, and Gibbs-indophenol. The vacuoles of the cells stain with scarlet red, Sudan IV, and osmic acid. They show doubly refractile crystals when examined by polarized light. Mucin has been demonstrated by Meyer's mucicarmine stain. The exact nature of the granules is still under debate.

The limitations of silver stains in establishing the diagnosis of carcinoid tumor particularly in rectal lesions have been recognized. Failure to demonstrate granules which can be blackened by the Masson or Gomori method does not mean that a tumor is not a carcinoid nor is a positive result unequivocal evidence that a tumor is a carcinoid, for several kinds of granules may give the argentaffin reaction. It should be emphasized that there are no characteristic histologic features which enable one to distinguish those carcinoids likely to metastasize from those which will not.

Multiple sites of origin. The tendency of multiple carcinoid tumors to develop from different areas of the gastrointestinal tract in the same individual has been noted in several reports. Ritchie in an extensive review of the literature in 1956 found that 28 per cent of small intestinal carcinoids were multiple but less than 10 per cent of other extra-appendicular carcinoids showed this tendency. As many as 68 presumably primary neoplasms have been found in 1 individual and in our institution we have treated a patient with 40 tumors (21). However, in our series of 25 rectal lesions no patient had more than 1 carcinoid tumor as best as we could determine.

Associated malignant tumors. In a review of 29 patients with carcinoid tumors found at necropsy, Pearson and Fitzgerald reported that 9 (31 per cent) had associated malignant gastrointestinal tumors of a different histologic type. Warren and Coyle found that 10 of 19 asymptomatic carcinoids (53 per cent) were associated with other malignant neoplasms and Foreman noted associated malignancy of a different type in 7 of 15 (47 per cent) cases of carcinoid tumors.

One patient in our series of 25 rectal carcinoids had an associated rectal polyp with malignant changes and 2 other patients had benign adenomatous polyps. All of the patients were subjected to sigmoidoscopy and to roentgenographic examination with a barium enema. The incidence of associated neoplasms in our group is much lower than that reported by some authors.

INCIDENCE, AGE, SEX, AND RACE

Carcinoid tumors are not common. A survey of surgical and autopsy statistics based on several large series of cases indicates an incidence of 0.08 per cent (138 carcinoids in 175,891 cases) with a range of 0.05 to 0.20 per cent. Only 1 out of every 15 to 20 gastrointestinal carcinoids occurs in the rectal area.

In 1957 Lamphier and Ehrlich were able to find reports of 212 cases of carcinoid of the rectum. These authors added 6 cases of their own and shortly thereafter Adamson and Postlethwait described 7 additional cases. With our 25 cases, 6 of which have been reported previously by Horn, the total number of cases is 244. This number undoubtedly represents only a portion of the rectal carcinoids which occur, since Freund

TABLE I.—AGE AND SEX INCIDENCE IN 25 CASES OF CARCINOID OF THE RECTUM

	No. cases	*Incidence, per cent*
Age, years		
20–39	4	16
40–59	13	52
60–79	8	32
Sex		
Male	15	60
Female	10	40

in 1957 was able to uncover 303 unreported cases by means of a questionnaire survey of 1,269 surgeons.

Gastrointestinal carcinoids have been observed in patients of all ages, from 10 days to 89 years. While carcinoid tumors of the appendix are found most frequently in young adults undergoing operations for appendicitis, extra-appendiceal carcinoids including those of the rectum usually are discovered during the fifth and sixth decades of life. Our 25 patients with rectal lesions ranged in age from 29 to 74 years, the average age being 53 years (Table I). Eighty-four per cent of the patients were over 40 years old.

Fifteen of the patients in our group were men and 10 were women, a difference which is probably of no significance. Fifteen patients were white and 10 were Negro. Neither sex nor race appears to influence the occurrence of carcinoid tumors.

CLINICAL FEATURES

The symptoms produced by gastrointestinal carcinoids vary with the location of the tumor. In the appendix the most common symptoms are those of acute inflammation, probably resulting from obstruction of the lumen. In the small bowel, symptoms of partial or complete intestinal obstruction are most frequent. Rectal carcinoids often cause no symptoms. Of our 25 patients with rectal tumors, 32 per cent had no complaints referable to the lesion and it was discovered only as a result of a routine examination or investigation of an unrelated abnormality (Table II).

TABLE II.—SYMPTOMS IN 25 CASES OF CARCINOID OF THE RECTUM

Symptoms	*No. cases*	*Incidence, per cent*
Asymptomatic	8	32
Hematochezia	6	24
Pain	6	24
Constipation	6	24
Weight loss	3	12
Change in bowel habit	2	8
Obstruction	2	8
Abdominal mass	1	4

The most frequent symptoms experienced by the 17 symptomatic patients were pain (24 per cent), rectal bleeding (24 per cent), and constipation (24 per cent). Other difficulties were weight loss (12 per cent), obstructive symptoms (8 per cent), diarrhea (4 per cent), and an abdominal mass (4 per cent). Most patients had more than one complaint. It is probable that in 4 of the 6 patients with pain, this symptom was due to a lesion other than the primary rectal neoplasm, and that 2 of the 6 patients with hematochezia bled from hemorrhoids rather than from the tumor.

Of some interest is the finding of other diseases of the lower gastrointestinal tract in 28 per cent of the 25 patients. These included hemorrhoids (8 per cent), adenomatous polyps (12 per cent), and diverticulosis of the colon (8 per cent). In most instances these associated abnormalities produced no symptoms and were discovered incidentally as a result of sigmoidoscopy and roentgenography with a barium enema.

MALIGNANCY

It was believed for many years that carcinoids rarely metastasize. More recent data, however, suggest that these tumors have a rather high malignant potential. The percentage of carcinoids which metastasize has been found to vary with their site of origin. Those most likely to spread originate in the small intestine while appendiceal neoplasms infrequently develop metastases. Perhaps this striking difference in malignancy may be attributed to the fact that lesions in the appendix are discovered in patients who are 20 to 30 years younger than those in whom extra-appendicular neoplasms are usually found.

As was mentioned previously, it is not possible to differentiate metastasizing and nonmetastasizing carcinoids on the basis of their histologic patterns. The great majority of these tumors appear benign upon microscopic examination. The most reliable indices of malignancy are microscopic evidence of local extension into and beyond the muscular coat of the bowel, and the finding of metastases in lymph nodes or other organs. While metastases have been found in almost every organ in the body, the most common sites of spread are the regional lymph nodes and the liver.

Carcinoids of the rectum generally have been regarded as lesions of low malignant potential which spread infrequently. Various authors have reported an incidence of metastases of 8 and 14.5 per cent. Diffenbaugh and Anderson calculated an incidence of spread of 13.8 per cent among 130 rectal carcinoids collected from the literature. The incidence of malignancy in our series is considerably higher than that previously reported.

In 10 of our 25 patients with rectal carcinoids evidence of malignancy was found, an incidence of 40 per cent. In all 10 cases extension of the tumor into or beyond the muscle coat of the bowel was demonstrated in the biopsy specimen obtained through the sigmoidoscope. Six of the 10 patients were found to have metastases when laparotomy was performed and in 1 additional patient metastases developed and death occurred 7 months postoperatively.

Since the size of the tumor appears to us to correlate with the behavior of rectal carcinoids, we have divided our cases into two groups based on the measurement by the pathologist of the largest diameter of the lesion (Table III). Of the 15 lesions which measured less than 2 centimeters in diameter, only 1 showed signs of malignancy. This tumor extended through the bowel wall but had not spread to lymph nodes or other organs. In contrast, 9 of the 10 tumors which measured 2 centimeters or greater in diameter were found to have metastasized and/or extended locally.

TABLE III.—RELATION OF SIZE TO PATHOLOGIC CHARACTERISTICS OF 25 CASES OF RECTAL CARCINOID

	Diameter of tumor	
	0.1–1.9 cm.	*2–2.9 cm.*
No. cases	15	10
Ulceration	0	3
Muscle invasion	1	9
Lymph node spread	0	9
Distant metastases	0	6
Per cent "malignant"	6.6	90

It seems probable that the size of the tumor is a reflection of the length of time during which the tumor has been present and that the time factor in turn strongly influences the opportunity of the lesion to spread. In our opinion the two characteristics of rectal carcinoids which should cause concern are microscopic evidence of invasion of bowel muscle and a size of 2 centimeters or greater in diameter.

THE MALIGNANT CARCINOID SYNDROME

In 1953 three groups of investigators independently reported the occurrence of unusual symptoms in patients with carcinoid tumors which had metastasized to the liver. Since then, numerous reports have appeared describing this syndrome which includes peculiar episodic flushing, telangiectasia and cyanosis of the skin, chronic diarrhea, dyspnea, and cardiac valvular disease involving

TABLE IV.—RESULTS OF TREATMENT IN 25 CASES OF RECTAL CARCINOID

Diameter of tumor, cm.	*Therapy*	*No. cases*	*Died of disease*	*Alive and well < 5 years*	*Alive and well >5 years*
0.1–1.9	Local excision	13	0	5	8
	Abdominoperineal resection	2	0	2	—
	Palliation	0			
2–2.9	Local excision	1	0	—	1
	Abdominoperineal resection	3	1	2	—
	Palliation	6	6	0	0

TABLE V.—SUMMARY OF 25 CASES OF CARCINOID OF THE RECTUM

Age Sex Race	*Symptoms*	*Diameter of tumor, cm.*	*Pathology*			*Treatment*	*Follow-up*
			Muscle invasion	*Lymphatic spread*	*Distant metastases*		
41 M W	Rectal bleeding	<1	0	0	0	Local excision	Living and well 6 yrs.
35 F W	None	<1	0	0	0	Local excision	Living and well 11 yrs.
56 F C	Constipation	<1	0	0	0	Abdominoperineal resection for ca. rectum (also present)	Living and well 4½ yrs.
53 M C	Rectal bleeding	1.5	0	0	0	Local excision	Living and well 5 yrs.
76 M W	Occ. constipation	2	0	0	0	Local excision	Living and well 8 yrs.
33 F C	None	1	0	0	0	Local excision	Living and well 8 yrs.
72 M W	Diarrhea	1	0	0	0	Local excision	Living and well 3½ yrs.
42 F C	None	0.5	0	0	0	Local excision	Living and well 6 yrs.
55 M W	None	1	0	0	0	Local excision	Living and well 14 yrs.
61 M W	None	0.5	0	0	0	Local excision	Living and well 5 yrs.
35 F W	None	<1	0	0	0	Local excision	Living and well 6 yrs.
54 M C	Abdominal pain; obstruction	>2	+	+	+	Exploratory laparotomy; transverse colostomy	Died of carcinoid 2 yrs.
41 F C	Change in bowel habit; abd. pain; mass	>2 (ulcerated)	—	—	+	Rectal and liver biopsy	Died of carcinoid 2 yrs.
72 M C	Change in bowel size; wt. loss; rectal pain	>2 (ulcerated)	+	+	0	Abdominoperineal resection	Died 6th po. day
51 M W	Rectal bleeding	2	+	+	+	Abdominoperineal resection	Died of carcinoid 7 mos.
29 F W	Wt. loss; back pain; constipation	3	+	+	+	Inguinal node biopsy	Died of carcinoid 9 yrs.
65 M C	Wt. loss; obstruction	>2	+	+	—	Exploratory lap.; colostomy	Died of carcinoid 2 mos.
54 F C	Abd. pain; constipation	<1	+	+	0	Abdominoperineal resection	Living and well 2½ yrs.
66 F C	Constipation	0.4	0	0	0	Local excision	Living and well 2 yrs.

TABLE V.—SUMMARY OF 25 CASES OF CARCINOID OF THE RECTUM (Continued)

Age Sex Race	Symptoms	Diameter of tumor, cm.	Pathology: Muscle invasion	Pathology: Lymphatic spread	Pathology: Distant metastases	Treatment	Follow-up
50 F W	Rectal bleeding	3	+	+	0	Abdominoperineal resection	Living and well 3½ yrs.
74 M C	Rectal bleeding	<2	0	0	0	Local excision	Living and well 1½ yrs.
73 M W	None	<2	0	0	0	Local excision	Living and well 6 mos.
43 M W	Rectal bleeding	>2 (ulcerated)	+	0	0	Anterior resection	Living and well 2 mos.
52 M W	None	0.2	0	0	0	Local excision	Living and well 1 mo.
40 M W	Constipation; epigastric pain	2.5	+	+	+	Exploratory lap.; biopsy	Died of carcinoid 1 yr.

the pulmonary and tricuspid valves most commonly and occasionally the mitral and aortic valves. In 1953 Lembeck established the chemical basis for the malignant carcinoid syndrome when he isolated 5-hydroxytryptamine (serotonin) from a malignant carcinoid. Subsequently, elevated blood levels of serotonin and elevated urine levels of its breakdown product, 5-hydroxyindole acetic acid, have been demonstrated repeatedly in patients who have metastatic carcinoid tumors and characteristic symptoms.

It is interesting that none of the cases of the malignant carcinoid syndrome reported in the literature has been associated with rectal carcinoids. Although in 6 of our 25 patients with rectal lesions extensive hepatic metastases developed, none of these patients was subject to any of the striking clinical phenomena caused by excessive production of serotonin.

TREATMENT

Carcinoid tumors of the rectum pose some difficult problems in therapy not encountered with most other gastrointestinal carcinoids. Because of the anatomy of the rectal area, the decision regarding the benignancy or malignancy of a given lesion usually determines whether the patient will be subjected to a simple local excision or to a radical abdominoperineal resection and permanent colostomy. The crux of the problem lies in our scant knowledge of the behavior of this neoplasm and the difficulty in determining its malignant potential.

In our series of 25 patients with rectal carcinoids, three forms of treatment were employed, namely, local excision, radical resection, and palliative measures (Table IV). Six patients were found to have distant metastases at the time of operation and received only palliative treatment, such as colostomy. All of these patients had large local lesions and all of them eventually died of cancer, 5 within 2 years of initial treatment. One patient, however, lived 9 years before succumbing to widespread metastases.

Fifteen patients had lesions which on examination of the biopsy specimen appeared to be confined to the submucosa of the bowel with no evidence of local or distant extension. Fourteen of these had tumors which measured less than 2 centimeters in greatest diameter and the other patient had a lesion the diameter of which was just 2 centimeters. One of these apparently benign neoplasms was treated by abdominoperineal resection, mainly because of an associated rectal polyp showing carcinomatous changes; the patient

has been well for 5 years since operation. The remaining 14 lesions were removed by local excision. All of these patients have maintained good health and have shown no signs of recurrence for from 1 month to 14 years postoperatively. Eight of these patients were treated more than 5 years ago.

In 4 patients histologic sections of the rectal biopsy specimens revealed extension of the neoplasm into the muscle layer of the bowel. The lesions in 3 of the patients measured greater than 2 centimeters in diameter. The finding of invasion was regarded as ominous, and accordingly all of these patients were subjected to abdominoperineal resections. At the time of operation, none of the patients had distant metastases, but 3 of the 4 were found to have neoplastic involvement of regional lymph nodes and in the other patient a serosal nerve bundle was invaded by the tumor. One patient died of widespread metastases 7 months after operation and the other 3 are alive and apparently free of disease 3½ years, 2½ years, and 2 months postoperatively.

As mentioned previously, the size of a rectal carcinoid appears to reflect its behavior, and this in turn influences treatment (Table IV). Fifteen of the patients in our series had lesions which measured less than 2 centimeters in diameter. Thirteen of these were treated by local excision, and none have recurred thus far. Two patients were subjected to successful radical resections, 1 of whom was so treated only because of an associated polyp containing cancer.

In contrast, 10 patients had tumors measuring 2 centimeters or more in diameter, and only 1 of these (which measured just 2 cm.) was treated by local excision. Six of the 10 were not candidates for curative therapy because of metastatic disease. The remaining 3 patients, all of whom had microscopic extension to regional lymph nodes, were treated by abdominoperineal resection and 2 of these are still alive and well.

Analysis of the results of treatment in our group of cases does not define with certainty the indications for either the radical or conservative treatment of rectal carcinoids. All of the cases which were treated by local excision appeared "benign" on microscopic examination of both the rectal biopsy and the excised specimen and none have recurred. On the other hand, it seems unlikely that those patients who were subjected to abdominoperineal resections would have done as well were they treated conservatively, since all of them were found to have local neoplastic extension in the rectal biopsy specimens, and all proved to have evidence of neoplastic disease in the regional lymph nodes. It would appear from our results that 2 factors should influence the choice of therapy. The most important of these is histologic evidence, obtained by sigmoidoscopic biopsy of the tumor, of extension of the carcinoid into or beyond the muscle coat of the bowel wall. We are of the opinion that this finding is an indication for abdominoperineal resection. Local excision would have failed to remove the neoplasm completely in every case in our series in which the biopsy revealed extension of the tumor into the muscularis. Although in each case we were fortunate in being able to determine from the biopsy specimen whether or not the neoplasm had extended locally, it is realized that this is not always possible.

The second factor, and one of less importance, is the size of the lesion. In our group, 14 of the 15 tumors which measured less than 2 centimeters in greatest diameter proved to be "benign," while 9 of the 10 lesions measuring 2 centimeters or greater were malignant and in fact had extended beyond the bowel. While we do not believe that large size is an absolute indication for radical treatment, the surgeon should be alert to the great possibility of malignancy in any tumor 2 centimeters or greater in diameter.

In our opinion the combination of a satisfactory biopsy specimen and an accurate appraisal of size serves as a satisfactory foundation upon which to base the choice of therapy in the majority of cases. It should be added that local recurrence of a rectal carci-

noid tumor is an indication for radical treatment.

Little has been written about the use of radiation in the therapy of gastrointestinal carcinoids. Our results with external radiation in several cases of metastatic tumor have been disappointing. It appears doubtful that carcinoids are radiosensitive neoplasms.

SUMMARY AND CONCLUSIONS

The clinical and pathologic characteristics in 25 cases of carcinoid tumor of the rectum treated at the Hospital of the University of Pennsylvania during a 25 year period have been reviewed in an attempt to shed some light on the behavior of this neoplasm. Analysis of these cases revealed that rectal carcinoids are found most frequently in middle-aged and elderly patients of both sexes. Histologically, they are identical to those found elsewhere in the gastrointestinal tract. However, the tendency of patients with gastrointestinal carcinoids to develop multiple argentaffin tumors as well as associated malignant lesions of different histologic types was not evident in our group.

The most frequent symptoms associated with rectal carcinoids were pain, bleeding, and constipation, each occurring in about one-fourth of the cases. One-third of the patients had no symptoms.

Forty per cent of the lesions in our series were malignant, a greater incidence than previously reported, and 24 per cent were incurable because of distant metastases. The incidence of malignancy appears to be related to the size of the lesion, since only 1 of 15 lesions measuring less than 2 centimeters in diameter showed malignant properties while 9 of 10 tumors which were 2 centimeters or larger were found to have extended locally or metastasized. Although in 6 cases extensive hepatic metastases occurred, no signs were detected of the malignant carcinoid syndrome caused by excessive serotonin.

Fifteen patients had benign lesions as determined by rectal biopsy and were treated by local excision of the tumor. All of these patients are alive and well, 8 of them more than 5 years postoperatively. Four patients showed evidence of local invasiveness on rectal biopsy and were treated by abdominoperineal resection. One of these patients died subsequently of metastases, and the other 3 are alive and in good health. The remaining 6 patients had distant metastases when first seen and succumbed to widespread neoplastic disease.

Our results suggest that two factors should influence the surgeon in the direction of radical therapy. These are evidence from a rectal biopsy of extension of the carcinoid into or beyond the muscle coat of the bowel and a tumor size of 2 centimeters or greater in diameter.

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THE EFFECTS OF IRRADIATION UPON THE REVASCULARIZATION AND SURVIVAL OF SKIN AUTOGRAFTS

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FOLLOWING various extirpative procedures it is occasionally necessary to close soft tissue defects by the use of skin grafts laid on sites which have previously been therapeutically irradiated. The survival of these skin grafts is notoriously hazardous, and failure is a not uncommon occurrence. The explanation of this failure to survive remains largely conjectural but is widely believed to be associated with certain vascular phenomena. Certainly, the survival of a skin graft, other factors being equal, depends on the effective transport of metabolites to and from the graft and its recipient site. In the initial or prevascular phase, this occurs by diffusion through a viscous, proteinaceous, extracellular fluid present at the interface—the "plasmatisch" circulation of Goldmann. After this initial phase, a characteristic vascular phenomenon occurs in which knoblike tufts of endothelium grow from the existing capillaries of the base and periphery of the recipient site in an orderly fashion toward the empty, widely patent vessels of the graft. Conway and associates have shown that successful grafts occur only when blood vessels of the recipient site remain patent, exhibit active circulation, and are able to proliferate actively.

The following study was undertaken for two reasons: (1) to determine if the profound changes wrought by roentgen irradiation upon a recipient site could affect the blood vessels of that site and therefore the revascularization and ultimate survival of a skin graft laid upon that site; and (2) to determine the optimum time, in terms of survival, for the performance of such grafting procedures.

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METHOD

Both ears of 20 albino rabbits of mixed stock were shaved and 3 circular pieces of skin approximately 12 millimeters in diameter were cut from the dorsum of each ear. The full thickness of skin was removed, care being taken not to damage the subcutaneous vascular plexus. The grafts from the left ear were sutured with No. 5-0 interrupted silk to the recipient sites upon the right ear. Those from the right ear were simply laid unsutured upon the recipient site of the left ear, their fate being unimportant to this investigation.

Since the rabbits made no attempt to dislodge the grafts, no dressings or splints were used. The absence of dressings permitted daily inspection of the grafts. At daily intervals following grafting, 4 to 6 milliliters of 4 per cent bromophenol blue were injected during a period of about 1 minute into the marginal vein of the ear. The dye solution was prepared by adding 15 milliliters of fifth normal sodium hydroxide to 1 gram of bromophenol blue and the total made up to 25 milliliters with 0.9 per cent sodium chloride solution. Normally vascularized tissues are colored intensely blue immediately after injection, the depth of the color being roughly proportional to the degree of vascularity. The immediate color change, which is due to the presence of dye within the blood vessels, is followed after several hours by the gradual appearance of a paler color resulting from the diffusion of the dye from the vessels into the

tissues. Avascular tissue fails to demonstrate the initial color response but becomes colored by diffusion after several hours. The only color changes recorded in this procedure were those occurring immediately after injection of the dye while the material is essentially intravascular. The dye is entirely harmless, and 24 hours later vascularized tissues are no longer colored. Dye disappears from nonvascularized tissues far more slowly, however, and 24 hours after the injection, nonvascularized skin grafts are still faintly blue. The color changes in the skin of the ear surrounding the grafts serve as controls. The term "vascularization time" as used herein is a measurement by inference and refers to the number of days which are required for the graft to achieve the same color intensity as the surrounding skin immediately after injection of dye. The term derives from the assumption that the intensity of the color change is in direct proportion to the vascularity of the graft.

After ascertaining that the average time required for revascularization of such grafts in a group of nonirradiated control animals was 4½ days, the time range was likewise determined in a group of irradiated animals. The right ears of 60 albino rabbits of varying ages were given sufficient radiation to produce a severe erythema. The dosage varied with the age of the animals, 3,500 roentgens being sufficient radiation for the youngest, while the largest and oldest required up to 3 times as much to produce the desired severe erythema. For each treatment 550 roentgens were delivered at: kilovolt peak, 60; milliamperes, 20; half value layer, 0.5 millimeter aluminum; target skin distance, 16 centimeters; field size, 15 centimeter circle. Skin grafts were then performed, as previously described for the control group, at 2 days and at 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 weeks after irradiation. Prior to the actual experiment the technique of grafting was developed to the point where it is believed that any failure of the grafts to survive resulted from the variables of the study and not from faulty technique.

RESULTS

Each of the subgroups evaluated in the bar graph (Fig. 1) represents a minimum of 18 grafts. In nonirradiated control animals, on the first day after the grafting operation, the grafts remain starkly white while the surrounding skin is colored intensely blue. On each succeeding day, immediately after the dye injection the grafts became increasingly blue until, on the fifth day, the color of the graft approximates that of the normal skin of the ear. Thus, by this method of measurement, effective revascularization of a skin autograft in a rabbit's ear occurs between days 4 and 5.

Immediately after irradiation, during the initial stage of erythema, the color of the grafts approximated that of the surrounding skin in only 3 days instead of the normal 4½ days. As the time interval following irradiation lengthened, the revascularization time approached that of the controls and then continued to increase beyond that of the controls until at 4 weeks, 2 grafts failed for the first time, while the remainder required 7 days to revascularize. At 6 and 8 weeks, 8 days for revascularization were required of those that survived, but an increasingly high percentage of these grafts failed. At 10 weeks, the percentage of graft survivals increased sharply and those which revascularized did so within 8 days. At 12, 16, and 24 weeks, there were no failures and the time required for revascularization decreased progressively toward normal. In each case in which a graft failed, its color immediately after injection never became more than faintly blue.

DISCUSSION

The earliest grossly visible changes in irradiated skin are erythema and edema. The capillaries are dilated and engorged, and endothelial permeability is known to be increased. That there is also an abnormally rapid ingrowth of vessels from the

recipient site to the graft at this stage is shown by the significant decrease in the time required for immediate color equalization of graft and recipient site. Both of these factors would tend to suggest an added measure of security for grafts done at this time.

Conway and his associates, in describing the normal response of blood vessels in a recipient site to the presence of a graft, observed a seemingly purposeful, directional budding of vessels in a parallel, orderly fashion from the base and periphery toward the graft. When the blood vessels are irradiated to a mild degree, or in the erythema stage after heavy irradiation, they exhibit a proliferative response manifested by a process of budding or sprouting in a manner similar to that seen in the formation of primordial blood vessels in the embryo. Thus, as Stricker points out, in the early stage of inflammation, blood capillaries resume embryonic qualities. The added presence of a graft appears to orient these vessels sharply toward the graft and reestablish early continuity of effective circulation. Parenthetically, it might be noted that vascular hyperplasia is apparently limited to capillaries since Maximow and Bloom observe that vessels having muscular and elastic fibers in their walls are devoid of this capacity.

At the posterythema stage of irradiation, or when a somewhat heavier dose is given, according to Arnold, endothelial cells show swelling, vacuolization, and pathologic mitotic or amitotic proliferation. These cells will prove unable to form new capillaries, and angioblastic formation, so necessary to the survival of a graft, will not occur. Thus, capillaries destroyed by irradiation will find no replacement. However, that this is not an all-or-none phenomenon is shown by the failure of some but not all of the grafts at this stage to survive. Those that survived required an abnormally long time to revascularize. As the interval following heavy irradiation is increased and the cumulative effect becomes pronounced, nearly all angioblastic activity is suspended and nearly all of the grafts at this stage failed.

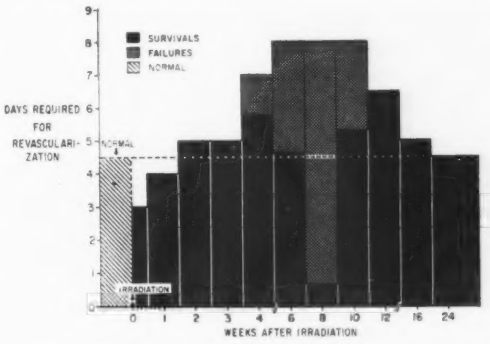

FIG. 1. Evaluation of revascularization of skin grafts after irradiation.

The late appearance of telangiectasia heralds the end of the inflammatory process and the restoration of capillary proliferation. The percentage of survivals increased, and revascularization time again reverted to normal.

SUMMARY AND CONCLUSIONS

An autogenous skin graft laid upon a rabbit's ear requires between 4 and 5 days to revascularize, as shown by the bromophenol blue dye technique. When roentgen irradiation in doses sufficient to produce severe erythema is first administered to an ear and then at varying intervals skin grafts are laid upon that ear, profound changes in revascularization time and percentage of survivals can be shown to occur. In the initial erythema-edema stage, effective revascularization occurs sooner than normal and all grafts survive, suggesting an added measure of protection for grafts done at this stage.

As the interval following irradiation lengthens, a progressively longer time is required for revascularization until ultimately nearly all the grafts fail. However, as the unique inflammatory response peculiar to irradiation subsides, angioblastic activity is again resumed in the recipient area and revascularization time and graft survivals again revert to normal. Thus, in the rabbit's

ear, there appears to be an early and a late optimum time for skin grafting after therapeutic irradiation as well as a time when grafts can be expected to fail.

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A METHOD OF PRODUCING RIGHT-SIDED CONGESTIVE HEART FAILURE IN THE DOG

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EXPERIMENTALLY PRODUCED congestive heart failure in animals provides a useful tool in the study of the physiology and pathogenesis of heart failure. Recently, it has enabled us to assess the effect of a partial venous to arterial extracorporeal bypass on the failing heart (9). Such assisted circulation has been employed by Harken and by Stuckey and associates in human beings with little success. An explanation for these poor results may lie in the lack of experimental work on the techniques of assisted circulation.

In the course of producing experimental heart failure with which to evaluate assisted circulation, several modifications of a technique originally described by Barger and associates (1, 5) have been developed. This technique, based on the staged production of tricuspid insufficiency and pulmonary artery stenosis, consistently produces right-sided congestive failure with increased venous pressure, sodium retention, ascites, edema, low fixed cardiac output, and loss of lean tissue. Because of the importance of this method in the evaluation of assisted circulation, because of its continued and potential value in other physiologic studies, and because the original operative technique has never been fully described, our modification of the Barger technique for producing right-sided congestive heart failure will be presented in detail, and its application to the study of assisted circulation in congestive failure will be discussed briefly.

TECHNIQUE

The first stage involves the creation of tricuspid insufficiency. Dogs larger than 15 kilograms are used to facilitate the intracardiac manipulation. The animal is placed in the left lateral decubitus position. A right thoracotomy is made in the fourth intercostal space. The pericardium is opened anterior and parallel to the phrenic nerve. Two opposing concentric purse-string sutures are placed at the base of the right auricular appendage. The tip of the appendage is amputated, and the right fifth finger is inserted into the auricle to assess the normal valve. This step facilitates subsequent evaluation of the completeness of valve destruction. The Barger valvulotome is then inserted as the purse-string sutures are tightened and held crossed by the assistant. With the fingers of the left hand placed against the right ventricle as a guide, the chordae tendineae of the anterior leaflet of the tricuspid valve are systematically engaged by the hooked blade of the valvulotome. Traction on the valvulotome avoids injury to the papillary muscles and puckers the ventricular wall, indicating that the hooked blade of the instrument has engaged the chordae (Fig. 1). The blade of the valvulotome is retracted into the sheath. As the blade is retracted, successful division of the chordae is indicated by a snapping sensation and by the indrawn ventricular wall rebounding against the fingers of the left hand. The posterior cusp is dealt with similarly. The small septal cusp is ignored since its destruction is hemodynamically unimportant, and since an attempt to destroy it may result in damage to the right coronary artery.

The right fifth finger is then inserted and swept around the valve orifice. Any remaining chordae can be felt and subsequently cut by reinsertion of the valvulo-

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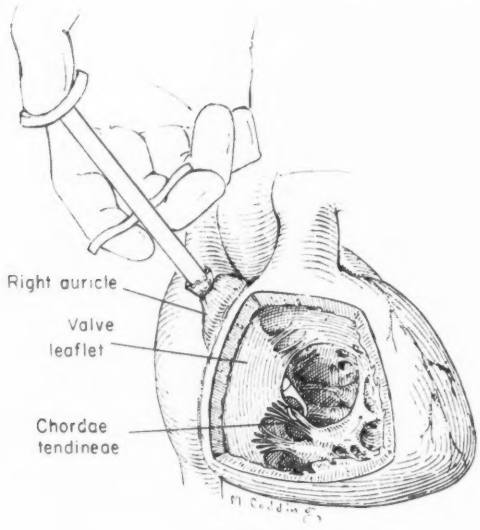

FIG. 1.

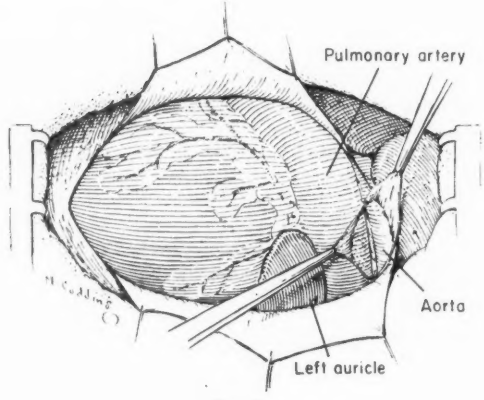

FIG. 2.

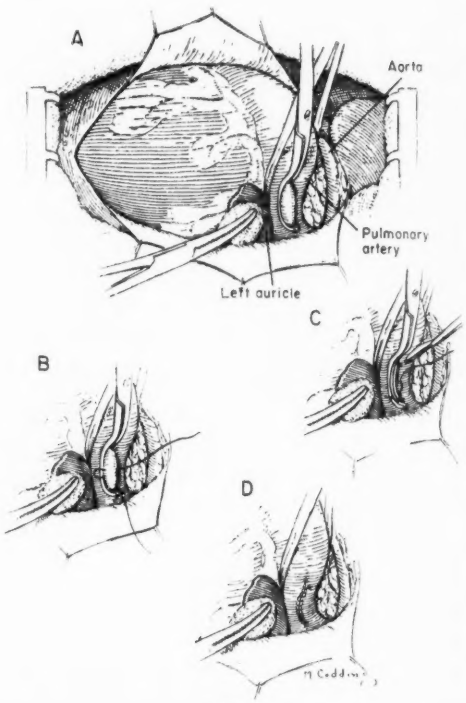

FIG. 3.

FIG. 1. Use of valvulotome. Double purse-string sutures in auricle maintain hemostasis. Valvulotome is inserted through auricle into ventricle. Blade hooks chordae.

FIG. 2. Pulmonary artery dissection. Cutting conus ligament allows entrance into avascular plane between pulmonary artery and aorta. By carrying dissection close to aorta isolation of pulmonary artery is safely executed.

FIG. 3. Pulmonary artery clamp. A, Applied to vessel. B, Horizontal running mattress suture placed inside clamp. C, Segment of vessel excised. Over and over running suture begun. D, Appearance of vessel after completion of operation.

tome. Mere production of an atrial bulge or thrill is a poor criterion of the adequacy of valve destruction. In fact partial interference with the function of one cusp can produce marked atrial pulsation and thrill without providing the necessary regurgitation.

When the chordae to the anterior and posterior cusps are destroyed, the purse-string sutures are tied and a tertiary ligature is placed around the base of the auricular appendage. The stump is oversewn, the pericardium closed loosely, the lung re-expanded, and the chest closed without underwater seal drainage. The animal is given penicillin and streptomycin for 3 days. Two to 3 weeks are allowed for recovery before proceeding with the second stage.

In the second stage, pulmonary artery stenosis is created. After the production of tricuspid insufficiency the animals are more sensitive to barbiturates, and only one-half of the original dose of intravenous pentobarbital (that is, 15 mgm. per kgm.) is used for anesthesia. When these animals are anoxic, arrhythmias are prone to develop.

Therefore, after the pentobarbital has been administered, endotracheal intubation with assisted respiration must be instituted promptly.

For the production of pulmonary artery stenosis a left thoracotomy through the fourth intercostal space is used. The pericardium is opened anterior to the phrenic nerve. The pulmonary artery is isolated by incising the conus ligament and dissecting in the avascular plane between the aorta and the pulmonary artery (Fig. 2). It is necessary to stay as close as possible to the aorta to avoid tearing the friable pulmonary artery. A tape is passed around the pulmonary artery to define its diameter. The pulmonary artery clamp is then applied to occlude the artery partially by reducing its diameter 45 to 60 per cent (Fig. 3). A running horizontal mattress suture is placed just inside the clamp, and the segment of vessel thus demarcated is excised. The cut edges of vessel are then oversewn and the clamp is removed. Since the pulmonary artery is so easily torn, care must be exercised to avoid injury to the vessel by overzealous tightening or twisting of the clamp. This fairly complex technique is necessary because a simple ligature constricting the pulmonary artery can produce necrosis of the vessel with hemorrhage. Moreover, it is difficult to gauge the degree of stenosis with accuracy. Closure of the chest and postoperative care are the same as for the first stage.

RESULTS

Twenty dogs have been operated on. Frank congestive failure with marked ascites has been produced in 15. The total operative mortality has been 25 per cent. No transfusions were required. Of the 5 dogs that died, 4 were among the first 6 of the series. These 6 were operated on before the technical details outlined had been evolved from the early failures and from work done on dog cadavers. Four of the 5 deaths might therefore have been avoided, if the procedure described had been followed. One dog died of hemorrhage from a lacerated pulmonary artery; 1, of ventricular fibrillation after cutting the right coronary artery in attempting to destroy the septal cusp; 1, of an overdose of barbiturate anesthesia; and 1, of inadequate oxygenation following the induction of anesthesia in the second stage.

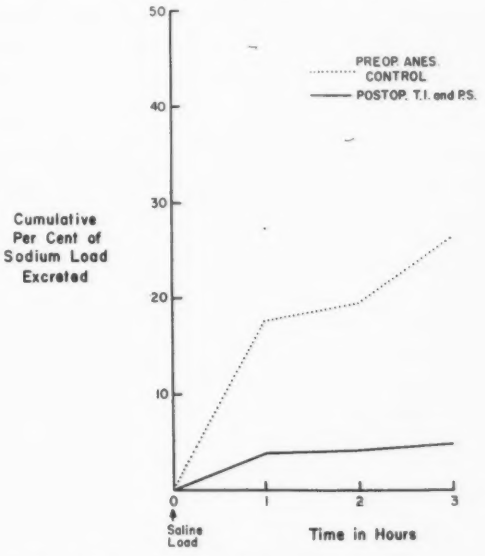

FIG. 4. Representative sodium excretions in response to a standard saline load in a typical anesthetized animal before and after production of combined tricuspid insufficiency and pulmonary artery stenosis.

DISCUSSION

Other techniques for producing experimental congestive failure have been described. Outstanding among these is the method of Davis which produces congestive failure by staged successive constrictions of the pulmonary artery. This technique, however, may require as many as 4 operations. Furthermore, the Barger technique continues to be the most reliable and is certainly the most thoroughly studied (2).

The production of chronic right-sided congestive failure in a laboratory animal by this technique provides a means for studying the complex and poorly understood mechanisms underlying this condition. Since

Barger's original work, much has been learned about the hemodynamic, renal, and endocrine factors inherent in this form of heart failure.

To evaluate the therapeutic effect of assisted circulation with the pump-oxygenator on chronic congestive failure, it is necessary to have a reliable index of the status of the heart failure over the short period for which assisted circulation is practical. The renal response to a standard saline load provides such a measure. This has been studied and standardized for normal dogs and for dogs in congestive failure due to tricuspid insufficiency and pulmonary artery stenosis (Fig. 4). We have, therefore, chosen the modified Barger technique described previously to produce congestive failure for the evaluation of the therapeutic effect of assisted circulation. The results of this study will appear in a subsequent communication (9). Since such assistance provides a means of temporarily reversing some of the hemodynamic alterations associated with congestive failure, it may further elucidate the complex pathogenesis of sodium and water retention in this condition.

That it can be adapted to the mitral valve adds further significance to the described method of creating tricuspid insufficiency. In the past, attempts to produce mitral insufficiency by other methods have met with little success since the amount of mitral valve destruction necessary to produce chronic failure must be critically gauged. The exact method of valve destruction permitted by the technique described may overcome this difficulty. Similarly, the stenosing technique outlined may have further use in the two staged procedures suggested by Muller and Sirak and their associates for the treatment of certain cardiac anomalies in infants too small to withstand early open heart surgery since the first stage of these procedures depends on the safe production of a critical degree of pulmonary artery stenosis.

SUMMARY

A detailed description of a technique for producing chronic right-sided congestive heart failure by creating tricuspid insufficiency and pulmonary artery stenosis is presented.

Important technical improvements that have been introduced are: a method for assuring effective tricuspid valve destruction with safety, a technique for safely isolating the pulmonary artery, and a new clamp for accurately stenosing this vessel.

Using the technique outlined in this article, the production of experimental congestive failure in dogs carries a mortality rate of less than 10 per cent.

The use of a standard saline load to evaluate the effect of assisted circulation on animals in heart failure created by this technique is discussed.

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TWO STAGE REPAIRS OF BENIGN STRICTURES OF THE BILE DUCT

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OUR EXPERIENCE with the general management of biliary stricture and the results following 802 operative repairs in 501 patients have recently been reported (1). The overall results in these 501 patients, following one or more operative repairs, have been satisfactory in approximately 70 per cent. In another article (2) the results following primary repair of biliary strictures in these patients have been described in detail. In the present report, those operative procedures in this group of 802 operations will be studied which were considered staged repairs. This category includes those patients in whom dilatation, a plastic procedure, or an anastomotic procedure carried out over an inlying Y or vitallium tube was performed, or in whom an external biliary fistula was produced as a first stage operation.

USE OF THE INLYING Y TUBE

The Y tube (Fig. 1) has been used to advantage as a prosthesis if the stricture in the duct was located close to the bifurcation of the common hepatic duct, and especially if the end of the proximal duct was not suitable for accurate suturing. Ordinarily in such instances the stricture is located within 1 centimeter of this bifurcation. These tubes serve to mold the anastomosis during the healing period and prevent its subsequent contracture. Some difficulty may be encountered in placing the Y tube within the reconstructed duct, particularly if the repair is made immediately below the bifurcation of the hepatic duct. Under these circumstances, the spur between the two hepatic ducts can be crushed and incised to give greater length to the common hepatic duct (Fig. 2).

It has frequently been necessary to remove these Y tubes a few months to several years after operation because of occlusion. Under such circumstances, removal of the Y tube is advised with exploration of anastomosis and removal of any accumulation of stones or detritus proximal to the tube.

INDICATION FOR ESTABLISHMENT OF EXTERNAL BILIARY FISTULA

Hepaticostomy (Fig. 3) has been used primarily for those patients whose condition precludes the extensive dissection required to effect a primary biliary anastomosis. In particular, hepaticostomy is recommended in those patients with severe degrees of liver damage and greatly elevated flocculation tests; in patients with high blood bilirubin levels, usually above 30 milligrams per 100 cubic centimeters; in patients with severe degrees of portal hypertension in whom operative hemorrhage impedes dissection; in patients whose general condition deteriorates

FIG. 1. Y tube which remained in place within hepaticojejunal stoma for 1 year.

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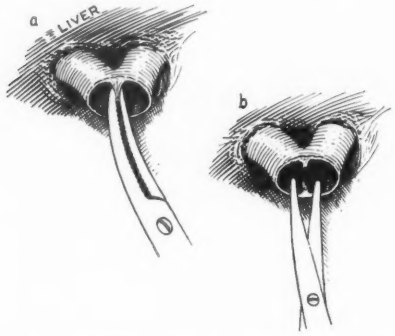

FIG. 2. a, Crushing, and, b, cutting spur of hepatic duct bifurcation.

during the course of attempted repair; and finally in the presence of sepsis in the subhepatic space. After external biliary diversion, the second stage procedure of anastomosis to the distal bile duct, jejunum, or duodenum is delayed for a period of 6 to 8 weeks or until optimum improvement has been attained.

In the course of 802 operative procedures for the relief of biliary stricture, the proximal end of the bile duct was not found in 12 instances. Under these circumstances, the placement of drains in the region of the porta hepatis has been followed at times by the establishment of an external biliary fistula along the course of these drains.

If biliary stricture occurs after operative procedures other than cholecystectomy (for example, gastric resection), the gallbladder is still intact in many cases. If the patient's condition precludes operative repair or anastomosis, then external decompression is accomplished by the performance of a cholecystostomy.

RESULTS

In the aggregate, the cases to be reported constitute the most difficult types of situations encountered by the surgeon in the repair of biliary strictures. The results of the staged Y-tube procedures are presented in Tables I and II. Eighty-eight hepaticojejunostomies over a Y tube (Fig. 4) were performed, with 3 postoperative deaths. Twenty-six patients have remained in satisfactory condition for 3 years or more and biliary obstruction has recurred in 45. Of these 45 patients, 19 cannot be considered in the evaluation of the second stage of the procedure because no subsequent operation has been performed, because operation was performed elsewhere, or because a new anastomosis was made instead of simply removing the Y tube. Transjejunal removal of the Y tube (Fig. 5) was carried out after hepaticojejunostomy in 26 patients, with poor results in only 2 instances. The remaining 24

TABLE I.—RESULTS OF 133 FIRST STAGE Y-TUBE PROCEDURES

		Dead		Alive		
Procedure	*No. of operations*	*Post-operative*	*Of disease*	*Poor*	*Satis-factory*	*Cannot evaluate**
Hepaticojejunostomy	88	3	6	45	26	8
End-to-end anastomosis	35	3	1	20	9	2
Hepaticoduodenostomy	6	1	1	0	3	1
Plastic or dilatation	4	0	0	4	0	0
Total	133	7	8	69	38	11

*The result has been satisfactory for less than 3 years in 9 of these 11 patients.

TABLE II.—RESULTS OF 36 SECOND STAGE Y-TUBE PROCEDURES

		Dead		Alive		
					Satisfactory	
Original procedure	*No. of operations*	*Post-operative*	*Of disease*	*Poor*	*More than 3 yrs.*	*Less than 3 yrs.*
Hepaticojejunostomy	26	0	0	2	11	13
End-to-end anastomosis	6	0	0	2	4	0
Plastic or dilatation	4	0	1	0	2	1
Total	36	0	1	4	17	14

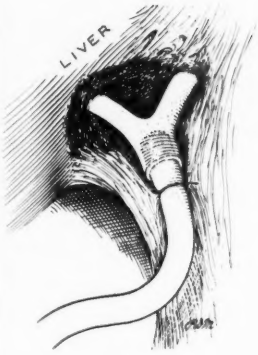

Fig. 3.

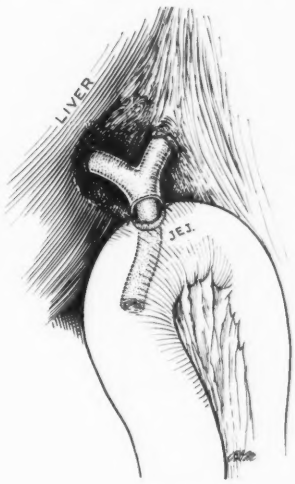

FIG. 4.

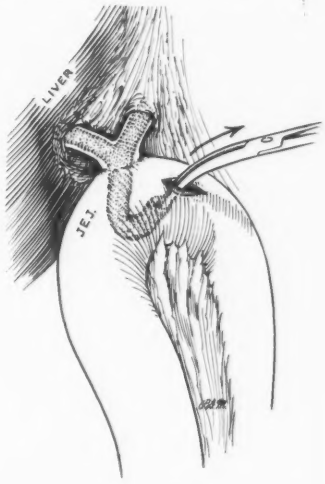

FIG. 5.

FIG. 3. Hepaticostomy.
FIG. 4. Hepaticojejunostomy over Y tube.

FIG. 5. Transjejunal removal of occluded Y tube from hepaticojejunostomy.

patients are alive and well—about half of them for longer than 3 years.

Of those 35 patients who had end-to-end anastomoses over Y tubes (Fig. 6), 3 died in the postoperative period; 9 have remained in satisfactory health for 3 years or more, and symptoms of biliary obstruction have recurred in 20. Of these 20, 14 cannot be considered in the evaluation of the second stage of the procedure for the same reasons as enumerated previously, after hepaticojejunostomy. The Y tube has been removed (Fig. 7) after return of symptoms in 6 patients, without any other procedure. Of these 6, 4 have had excellent health for 3 years or more and 2, recurrent symptoms.

Y tubes have also been used as a prosthesis after hepaticoduodenostomy in 6 patients, after dilatation of very high strictures of the common hepatic duct in 2 patients, and after plastic procedures on strictures high in the common duct in 2 patients. Excellent results were obtained after this procedure in 3 of the 6 patients submitted to hepaticoduodenostomy. Two patients died, but not because of failure of this type of repair. All 4 patients submitted to dilatation or plastic procedures over a Y tube experienced recurrent symptoms postoperatively. The second stage, or removal of the Y tube alone, was performed in these same 4 patients, with satisfactory results in 3.

In summary, approximately 30 per cent of patients remained free of biliary tract symptoms after the use of Y tubes as prostheses in conjunction with stricture repair. Of the 69 patients (52 per cent) in whom subsequent procedures were required, removal of the Y tube only was carried out in 36. After this second stage of the two stage procedure, only 4 of 36 have experienced recurrent symptoms.

The compilation of the eventual fate of the Y tubes is of interest (Table III). Definite information is available that only 17 of the 133 tubes used passed spontaneously into the intestine. These tubes may pass at

TABLE III.—FATE OF Y TUBES

Procedure	*No. of operations*	*Passed*	*Occluded*	*No information*
Hepaticojejunostomy...	88	14	32	42
End-to-end anastomosis.	35	2	14	19
Hepaticoduodenostomy..	6	1	0	5
Plastic or dilatation.....	4	0	4	0
Total.....	133	17	50	66

FIG. 6. End-to-end anastomosis over Y tube.

any time from approximately 1 month postoperatively up to 6 years in 1 instance. It is apparent (Table III) that this happened more frequently after hepaticojejunostomy than after end-to-end repair. On the other hand, 50 of 133 tubes became occluded and had to be removed surgically. In 4 instances, these tubes migrated from their original position without passing into the intestine. In 1 case the tube migrated proximally into the liver and was visible on the plain roentgenogram of the abdomen. At 2 subsequent surgical procedures, however, the tube could not be found. One tube became occluded and eroded into the duodenum. A third tube became plugged and slipped into the distal end of the bile duct after an end-to-end anastomosis. A fourth tube slipped out of the bifurcation of the duct and into the common hepatic duct above a hepaticojejunostomy. No information is available as to the fate of the other 66 tubes because the patients are either living and free of symptoms or have been lost to follow-up.

The fact that these Y tubes pass spontaneously does not in itself mean that the outcome will be favorable. Fourteen Y tubes passed spontaneously after their use in hepaticojejunostomy, and 7 of the patients subsequently suffered a recurrence of the partial obstruction to the biliary tract.

Various types of Y tubes have been used in the past. Originally, Y tubes made of bouncing clay or vitallium were favored. Within the last 10 years we have come to prefer tubes made of rubber to which lately barium (up to 20 per cent) has been added. These tubes are more flexible and more easily introduced into the upper ducts. In addition, the barium content enables visualization on the plain roentgenogram of the abdomen (Fig. 8).

Straight vitallium tubes have been used in conjunction with biliary tract procedures in 31 instances (Tables IV and V). The result was satisfactory in 7 of these 31 patients. In 9 second stage removals of the vitallium tube, 7 patients remained in satisfactory condition for more than 3 years postoperatively.

Table VI contains information regarding the fate of these vitallium tubes. Seven of 31 were known to have been passed spontaneously and 13 were removed because they became occluded with biliary detritus.

The immediate and later results following hepaticostomy, cholecystostomy, or failure to find the proximal duct and placement of drains in the porta hepatis are presented in Table VII. Because of the pre-

TABLE IV.—RESULTS OF 31 FIRST STAGE VITALLIUM TUBE PROCEDURES

Procedure	*No. of operations*	*Dead*		*Alive*		*Cannot evaluate*
		Post-operative	*Of disease*	*Poor*	*Satisfactory*	
End-to-end anastomosis	15	0	0	9	5	1
Hepaticojejunostomy	3	1	1	1	0	0
Hepaticoduodenostomy	3	0	0	2	1	0
Plastic or dilatation	10	1	0	8	1	0
Total	31	2	1	20	7	1

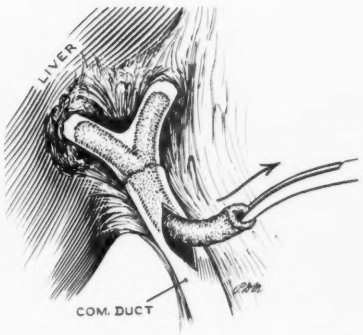

FIG. 7. Removal of occluded Y tube from end-to-end anastomosis.

FIG. 8. Y tube in place in hepaticojejunostomy.

carious general condition of these patients, the postoperative mortality following such procedures is appreciable. Of those 25 patients submitted to hepaticostomy, 4 died in the immediate postoperative period; only 5 have been salvaged and are alive with excellent results. In these 5 patients, 12 additional operative procedures were required to establish adequate biliary drainage into the gastrointestinal tract. Cholecystostomy was performed in only 1 case, and that patient is alive and well 12 years after the last operative procedure. Four of 12 patients died in the postoperative period after failure to locate the proximal duct. Of those patients in whom the upper ducts were not found, only 2 have been salvaged after 3 and 2 subsequent operative procedures, respectively. These are desperate situations and it is perhaps remarkable that such a high rate of salvage was eventually obtained.

DISCUSSION

Our preliminary results with the use of staged anastomotic procedures using Y-shaped rubber tubes as prostheses have been most satisfactory. Strictures involving, or adjacent to, the bifurcation of the hepatic ducts constitute the indication for the use of these tubes. These types of strictures are among the most difficult to manage surgically. Approximately one-third of all the patients in whom Y tubes were used did not require further operative procedures within the time limits of our follow-up study. Of those 36 patients in whom occluded Y tubes were removed, satisfactory results have been obtained in the vast majority (31). To be sure, a large number of these patients have had follow-up periods of less than 3 years, 14 of 31. It would be very surprising, however, if recurrences in these 14 patients amounted to an appreciable proportion.

In a few instances Y tubes have been used with an external T-limb extension. This external limb allows the tube to be removed without another operative procedure if it becomes occluded. It has been our experience, however, that this type of tube has been limited in application. The extreme variation in ductal length and configuration encountered in the repair of strictures

TABLE V.—RESULTS OF 9 SECOND STAGE VITALLIUM TUBE PROCEDURES

		Dead		Alive	
Original procedure	*No. of operations*	*Postoperative*	*Of disease*	*Poor*	*Satisfactory more than 3 yrs.*
End-to-end anastomosis	4	0	0	0	4
Plastic or dilatation	5	1	0	1	3
Total	9	1	0	1	7

TABLE VI.—FATE OF VITALLIUM TUBES

Procedure	*No. of operations*	*Passed*	*Occluded*	*No information*
End-to-end anastomosis	15	2	7	6
Hepaticojejunostomy	3	1	0	2
Hepaticoduodenostomy	3	3	0	0
Plastic or dilatation	10	1	6	3
Total	31	7	13	11

TABLE VII.—RESULTS AFTER EXTERNAL DRAINAGE

Procedure	*No. of operations*	*Dead*		*Salvage* (alive and well)*	*Cannot evaluate†*
		Post-operative	*Of disease*		
Hepaticostomy	25	4	10	5	6
Cholecystostomy	1	0	0	1	0
Ducts not found	12	4	5	2	1
Total	38	8	15	8	7

*Twenty subsequent operations were required in these 8 patients.
†Because another first stage procedure was required, no follow-up, or no second stage procedure.

causes technical difficulties in the use of this type of prosthesis. Furthermore, stones are often found proximal to occluded tubes, and operative removal of these tubes allows proper removal of any obstructing calculi.

There has been some reawakening of interest in the use of Pearse's straight vitallium tube prostheses in the repair of bile duct strictures as seen in the study by McGoon and Clagett. We have used these tubes to splint anastomoses located in the midportion of the common duct, but now favor T tubes instead, with the external limb brought out either above or below the site of repair.

As experience is gained in the operative management of biliary stricture, the number of cases in which the ducts cannot be found decreases. In 802 operations for stricture the upper end of the bile duct could not be found in only 12 instances. In many of these cases, the operating time was cut short by progressive deterioration in the patient's condition. In other instances, profuse hemorrhage from dilated venous sinuses resulting from portal hypertension precluded the advisability of further search for the duct. Under these circumstances, the placement of catheters and drains in the region of the porta hepatis has sometimes resulted in the formation of external biliary sinuses along these tracts. We have had only a limited experience with Longmire's procedure of intrahepatic cholangiojejunostomy. It is conceivable that this procedure would be of use under such circumstances. In these 12 difficult cases, it was possible to salvage 2 patients who are at present alive and free from symptoms. The indication for hepaticostomy has been discussed previously in this article. It is to be emphasized that these cases are among the most critical types, and it is surprising that 5 of the 25 patients in this category are now alive and well.

SUMMARY

The indications for and results with two stage repairs of bile duct strictures have been reviewed. This series has included: 12 cases in which the ducts were not found but an attempt at external fistula formation was made by the placement of drains and catheters in the hilus of the liver; 26 cases of external biliary diversion; and 133 cases in which anastomosis, a plastic procedure, or dilatation was performed over a Y tube. In addition, we have reported on the results of our experience with the use of straight vitallium tubes in 31 cases, although this prosthesis is no longer used. Our results with the use of these procedures have been most satisfactory in view of the fact that these strictures are the most difficult type to deal with because of their high location in the biliary tree. Approximately one-third of the patients in whom Y tubes were used experienced no further trouble related to the biliary stricture, and, of 36 patients in whom the Y tube became occluded, requiring removal, 31 are free of symptoms—17 for more than 3 years.

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HISTOLOGIC SEQUENCES FOLLOWING IMPLANTATION OF THE AUTOLOGOUS CANINE RIB INTO THE SPLEEN

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SOLUTION of the homograft rejection mechanism, although of tremendous importance, will not in itself guarantee the successful transplantation of many tissues. It must first be demonstrated that autotransplantation of a particular tissue will succeed before homotransplantation of the tissue in question is even considered. A case in point is the adrenal gland. For many years failure attended attempts at autotransplantation of the adrenal gland in dogs. Eventually, however, techniques were described which permitted viable transplants of both cortex and medulla. In a recent report on pancreatic transplantation Brooks and Gifford mentioned that the autotransplanted pancreas soon loses exocrine function unless the transplant is stimulated. Obviously, thorough familiarity with the fate of autotransplanted tissue is a *sine qua non* to successful foreign transplantation.

It has been suggested by Kurnick and associates that stored autologous bone marrow is useful in the treatment of hematopoietic depression induced by irradiation or nitrogen mustards; however, little is known about the actual cytologic and biologic events which take place after the administration of autologous bone marrow and the repopulation and proliferation of transplanted hematopoietic cells.

In view of this lack of information on autologous marrow growth, it seemed important to develop a technique allowing autologous marrow transplants to proliferate in an ectopic locus. In such an area the behavior of transplanted hematopoietic cells could be accurately followed up and observed. Since the spleen in the embryo is a blood-forming organ and since, under certain forms of stress in adult life, it supports extramedullary hematopoiesis, this organ was selected for experimental autologous marrow transplantation. The canine spleen with its long pedicle and easily isolated vasculature seemed especially well suited to house an in vivo culture of bone marrow.

METHOD

Under nembutal anesthesia operations were performed on mongrel dogs weighing between 35 and 45 pounds. After an incision was made over the left eighth or ninth rib and the periosteum was reflected, a 10 centimeter section of rib with its contained marrow was removed and covered with sponges soaked in normal saline. The chest wound was then sutured and the rib refrigerated at 4 degrees C. At this point the animal was given 150 roentgens of total body irradiation in air using a thoraeus 2 filter, 0.4 tin, 0.25 copper, 1 aluminum; distance of 76 centimeters 15.5 roentgens for 1 minute.

Following irradiation, the abdomen was opened through a midline epigastric incision and the spleen, on its long pedicle, was delivered out of the wound. The rib portions were then bisected longitudinally with bone shears and further divided into halves, 5 centimeters long. One end of each portion was sharpened and 4 such pieces were in-

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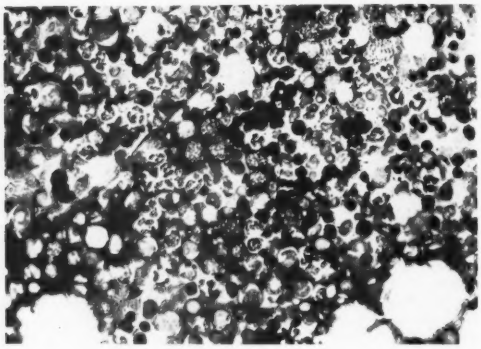
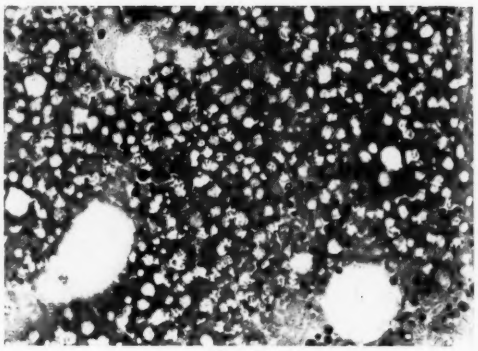


FIG. 1.



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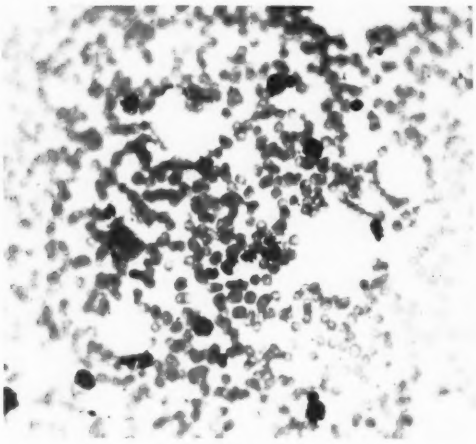


FIG. 3.

FIG. 1. Control marrow. Wright stain, ×245.

Fig. 2. Marrow removed 6 hours after insertion into spleen. Note early disintegration. Wright stain, ×245.

FIG. 3. Marrow removed from splenic site 18 hours after implantation. Wright stain, ×315.

serted into the splenic substance from the upper edge at right angles to the long axis of the spleen. Usually the small wounds of entry did not bleed excessively, but occasionally a suture was required to control the bleeding.

For a study of marrow growth after a planned interval, it proved to be a simple procedure to remove an implanted rib and effect hemostasis with either pressure or a hemostatic chromic suture. In some animals, ribs were inserted into the rib bed, kidney, liver, omentum, abdominal musculature, and subcutaneous tissue.

When the ribs with their contained material were removed, smears were taken for a study of marrow proliferation, and the entire split rib was fixed in Zenker's solution for histologic evaluation. Hematopoietic cells on smear stained with the Wright method were readily indentified, and marrow proliferation was recognized by the presence of rare myeloblasts, promyelocytes, myelocytes, and metamyelocytes as well as more mature neutrophilic, eosinophilic, and basophilic granulocytes. Proerythroblasts, normoblasts, megakaryocytes, clumps of osteoblasts, and occasional osteoclasts were also present.

Histochemical methods were employed further to study and identify hematopoietic cells. The cobalt-calcium technique of Gomori was used for alkaline phosphatase activity. Mature neutrophils in canine peripheral smears exhibited only a slightly positive alkaline phosphatase reaction; however, in marrow smears the more immature myeloid cells (myelocytes, metamyelocytes) as well as osteoblasts showed considerable cytoplasmic alkaline phosphatase activity. The peroxidase reaction described by Graham-Knoll (4) was positive in all but very immature myeloid cells; osteoblasts and other marrow cells were negative for this reaction. Further identification of myeloid elements was obtained by the use of a histochemical technique utilizing naphthol chloroacetate as a substrate. With this method all myeloid cells except myeloblasts in dog marrow

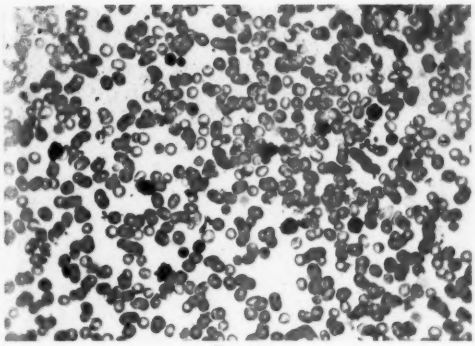


FIG. 4.

FIG. 4. Twenty-four hours after marrow insertion. Disappearance of marrow practically complete. Wright stain, ×245.

FIG. 5. Three days after insertion into spleen. Wright stain, ×315.

FIG. 6. Marrow 7 days after splenic implantation. Note primitive cell at 9:00 and osteoblasts at 1:00 and 5:00. Wright stain, ×315.

showed a strong esterase activity demonstrated by an intense red granular staining of the cytoplasm.

RESULTS

In all 20 animals subjected to this technique definite marrow proliferation was present in the rib cavity at the end of 6 weeks. This persisted for at least 1 year, the longest period that these animals have been observed to date. The split rib in the spleen remained intact.

In the beginning of these experiments, it was believed that the autologous marrow merely continued to proliferate in the spleen (Fig. 1). Serial investigation of the transplants revealed that such was not the case. Cytologic and histochemical methods showed that 6 hours after the implantation of autologous rib with its contained marrow into the spleen, the marrow cells were undergoing disintegration (Fig. 2). The disappearance of the marrow continued at a rapid rate (Figs. 3 and 4). Within 72 hours the specimens were markedly hypocellular (Fig. 5) showing only scattered primitive mononuclear cells and small groups of osteoblasts. Histochemical studies identified the osteoblasts by their intense alkaline phosphatase activity, but the primitive mononuclear cells containing a large nucleus with several nucleoli showed no evidence of alkaline phosphatase, esterase, or peroxidase activity. Specimens obtained on the seventh postoperative day presented a picture similar to the third day in all sites (Fig. 6). It was not until the eleventh to fifteenth day that a few immature myeloid and erythroid cells could be found (Fig. 7). Simultaneously, new bone formation was demonstrable on histologic section. Four to 6 weeks after implantation full blown marrow proliferation was observed (Figs. 8, 9, 10, and 11).

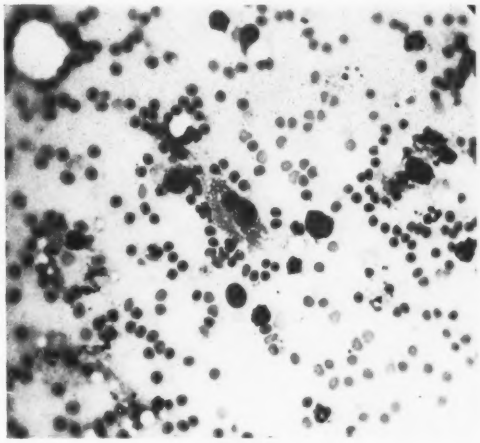
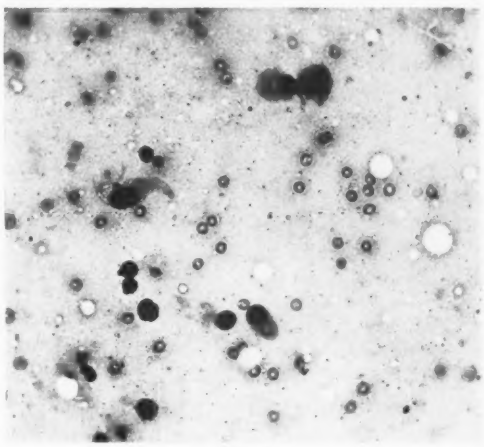


FIG. 5.



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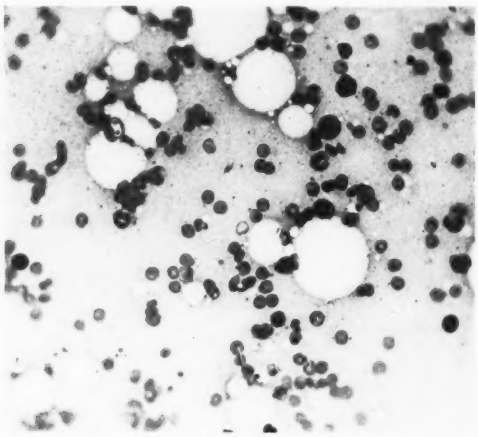
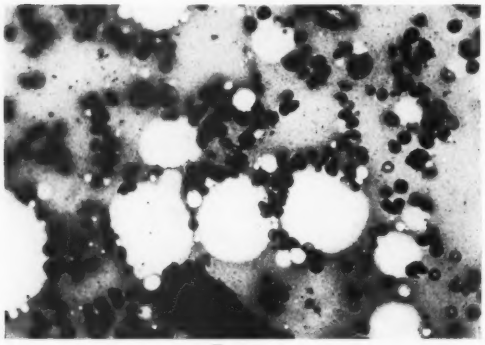


FIG. 7.



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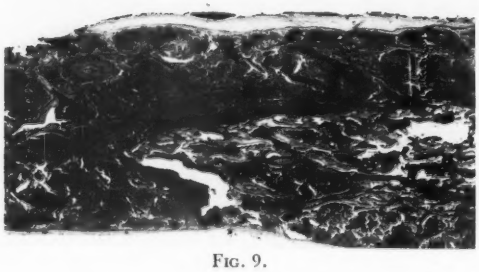

FIG. 9.

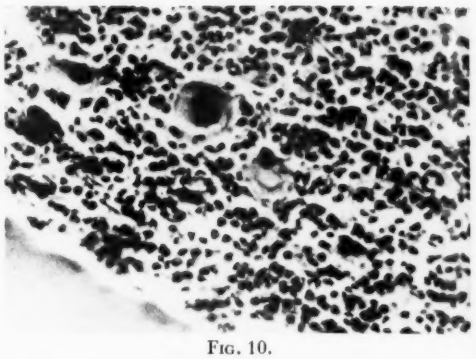

FIG. 10.

FIG. 7. Eleven to 15 days after threading of autologous rib with contained marrow into spleen. Earliest return of red and white cell precursors. Wright stain, ×315.

FIG. 8. Twenty-eight day specimen. Esterase stain, ×245.

FIG. 9. Six weeks after splenic insertion. Splenic capsule, pulp, and implanted rib with contained marrow. Hematoxylin and eosin, ×20.

FIG. 10. High power view of Figure 9 showing decalcified bone and cellular marrow with megakaryocytes. Hematoxylin and eosin, ×245.

Note that the 8 months' marrow presented a more hyperplastic picture than the control (Fig. 12), as did the 1 year specimen (Fig. 13).

The presence of these large primitive mononuclear cells on about the third post-transplantation day was difficult to interpret as the cells are not readily identifiable. As shown in Figures 5 and 6, these cells look like histiocytes and have a large amount of cytoplasm which is often vacuolated and "streaming" in character. These cells (Fig. 14) usually possess a single, vesicular, spongy-looking nucleus with 1 to 3 nucleoli and, unlike the osteoblasts, show no evidence of alkaline phosphatase. They are also devoid of peroxidase and esterase activity.

The nature of these primitive cells remains obscure. They may be primitive precursor cells for the marrow elements. On the other hand, they could represent tissue mesothelial cells which are emerging in response to necrosis and injury as phagocytic histiocytes. In favor of the precursor nature of these cells is the fact that, although present in homologous bone marrow transplants to the spleen at the end of 3 days, they have completely disappeared by the seventh day despite continued degeneration of the homologous transplant. Studies are under way to determine not only the function of these cells but also the source. Most likely they

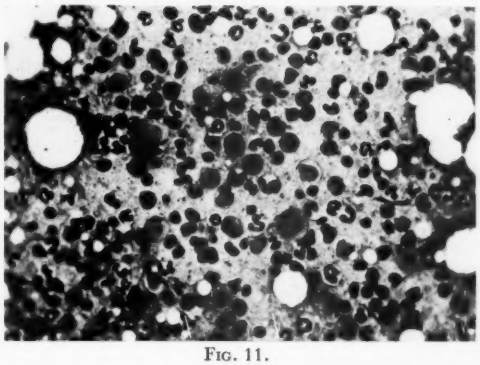

FIG. 11.

FIG. 11. Six weeks after splenic implantation. Wright stain, ×245.

FIG. 12. Eight month specimen. Wright stain, ×315.

FIG. 13. One year after splenic insertion. Wright stain, ×245.

FIG. 14. Cell shown may represent precursor of canine marrow elements. Wright stain, ×485.

originate from the autotransplant, but a host contribution cannot be ruled out at this time.

DISCUSSION

When an autologous rib with its contained marrow is implanted in the canine spleen, definite proliferation of marrow occurs. The spleen appears to be a more favorable site than liver, kidney, omentum, muscle, or subcutaneous tissue. To date we have been unable to effect marrow growth in the spleen by direct insertion of marrow without bone into the splenic substance or by injection of saline suspended marrow into the splenic artery.

The phenomenon of extramedullary hematopoiesis here described is favored by small doses of total body irradiation but will occur in 75 per cent of nonirradiated animals. Homologous bone with contained marrow will not proliferate nor will autologous bone alone, without periosteum or endosteum, grow marrow in our preparation.

Originally, efforts were made to destroy the canine marrow with large doses of myleran and then effect survival of the dog by implanting autologous marrow in the spleen. The animals died within 2 weeks.

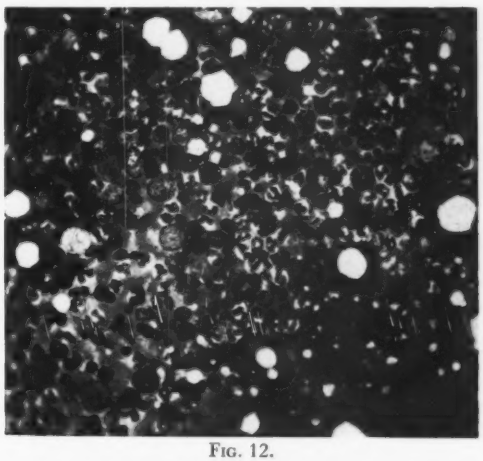

FIG. 12.

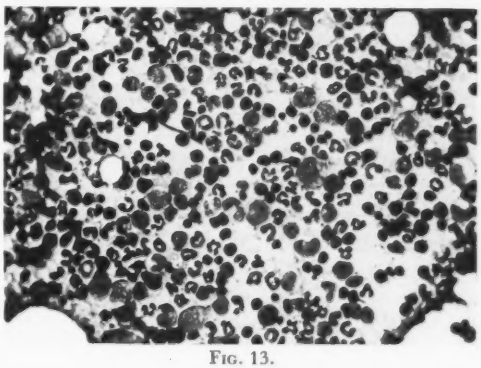

FIG. 13.

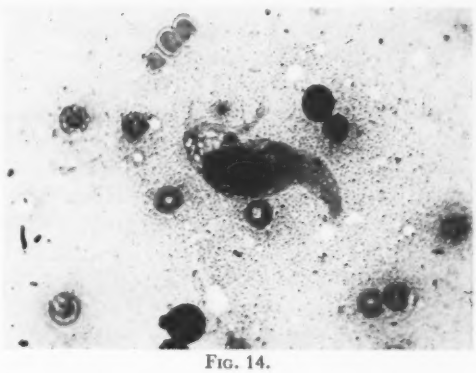

FIG. 14.

Our failure to protect dogs subjected to lethal doses of myleran with autologous marrow served as the impetus for this sequential study. A period of 4 to 6 weeks exists

before autologous marrow inserted into the spleen or omentum might be said to be in full proliferation.

While this work in dogs cannot be directly extrapolated to clinical problems, nevertheless the existence of this latent period with its characteristic hypocellular state may well occur in man and should be taken into consideration when marrow administration is contemplated.

CONCLUSIONS

1. A technique which permits the sequential observation of bone marrow proliferation in an ectopic site has been presented.

2. Autologous bone marrow implanted into the canine spleen, omentum, or rib bed disappears within 3 to 7 days.

3. A period of 4 to 6 weeks after transplantation is required before full blown proliferation of autologous marrow is seen.

4. A mononuclear cell which may represent the primitive precursor of all marrow elements in the dog has been described.

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A MECHANICAL URETERAL VALVE

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DYSFUNCTION of the ureterovesical junction continues to be a problem of major degree in urologic practice. In children with long-standing outlet obstruction or persistent infection, and sometimes for unexplained reasons, changes develop in the upper urinary tract which adversely affect function because of the reflux of urine from the bladder. Adults with bladder outlet obstruction, chronic infection, and neurogenic bladder difficulties show progressive renal deterioration because of incompetency of this normal valvelike arrangement. Attempts at construction of an artificial reservoir for patients whose bladders are removed or destroyed by disease have repeatedly been unsuccessful because of ureteral reflux and the transmission of pressure and infection to the renal parenchyma from the "bladder."

The classic course of a patient whose ureters were apparently connected to the gastrointestinal tract was described in the *Philosophical Transactions* of 1713, as pointed out by Richardson, where it was stated:

> . . . one John Woosnape of North Bierley, a poor boy, lived till he was 17 years of age and never made water and yet was healthy, vigorous and active. He had constantly diarrhea on him, but without much uneasiness. . . . He died of a fever.

Early experiments in animals by Glueck and Zeller, Bardenhauer, Novaro, Tuffier, Tizzoni and Pozzi, Paoli and Busachi resulted either in peritonitis or hydronephrosis with ureteral stenosis and fatal renal infection after ureterointestinal anastomosis. Van Hook and Chaput were not more successful although the former employed the anchor suture later used by Coffey. Krynski applied the Witzel technique in ureteral implantation and was able to prevent ascending infection in some of the animals. By 1900, according to Peterson, only 10 of 68 dogs in whom ureterointestinal anastomosis had been performed survived the immediate postoperative period.

Implantation of the ureters into the bowel in man was first reported by Simon in 1852. The patient died 1 year after operation with renal and ureteral calculi. The first extraperitoneal ureterocolonic anastomosis was performed by Smith (40) in 1878 on a 7 year old boy with exstrophy of the bladder. This patient died shortly after operation from uremia. In 1894, Maydl suggested transplantation of the entire trigone to preserve the normal ureterovesical junction and thus prevent reflux. By 1900, 36 such operations had been performed with only 2 deaths reported from ascending infection. Boari devised a button to be used by the extraperitoneal route and operated successfully on 1 patient. The immediate mortality of patients operated upon in the early years of the ureterointestinal anastomosis was 33 per cent, and the longest survival was 8 years. The development of the operative technique was described excellently by Hinman (17) and extensive reviews of the early literature were given by Peterson, Connell, and Steinke.

INCIDENCE AND ETIOLOGY OF URETERAL REFLUX

Increasing use of cystography, delayed cystograms, and voiding cystourethrograms has emphasized that the incidence of the phenomenon of ureteral reflux is much greater than had been previously appreciated. In 1916, Kretschmer reported finding reflux in 3 of 10 supposedly normal children

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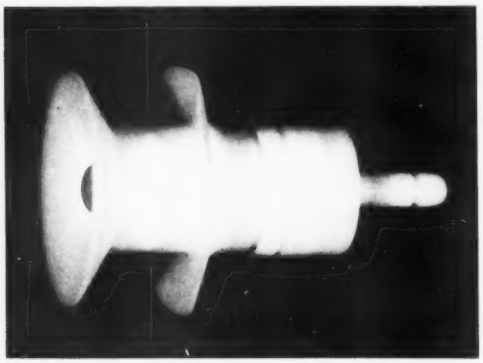

FIG. 1. Teflon valve. The two flanges are placed on either side of the bladder wall at surgery by means of a purse-string suture. The slender proximal tip is introduced into the ureter and secured by 2 silk sutures.

(22, 23). Campbell in 1937 reported an incidence of 12 per cent reflux in 722 infants. He suggested that reflux might be due to infection which converted the lower ureter into a rigid tube. Elimination of infection has cured some reflux but this is not always the solution. Bladder outlet obstruction is known to cause reflux, but removal of the obstruction does not always correct the situation. Bors reported that reflux was altered in only one-fourth of 24 patients who underwent transurethral resection of the vesical neck for bladder outlet obstruction. Investigation into the etiology and mechanism of ureteral reflux was reported by Gruber (14, 15) who upon distention of the bladder of an anesthetized animal was able to produce reflux presumably on the basis of reducing muscle tone in the bladder wall. The incidence of reflux was inversely proportional to the thickness of the bladder wall. Further experiments by Semblinov, Levin and Goldschmidt, Wislocki and O'Connor all demonstrated ureteral reflux in anesthetized animals. Thinning of the bladder wall was emphasized as an important factor by Hutch (19, 20) who reported the presence of a cellule in the trabeculated bladder of paraplegics immediately behind the intravesical portion of the ureter. He reported the incidence of ureteral reflux in these patients to be between 10 and 15 per cent. Bumpus observed reflux in 89 cases (8.5 per cent) in 1,036 random cystograms performed. In 527 patients with benign prostatic hypertrophy the incidence of reflux was 4.7 per cent. Bors found an incidence of reflux of 23 per cent in 238 patients with spinal cord disease or spinal cord injury, and Talbot and Bunts reported a 5 per cent incidence of ureteral reflux in 33 paraplegics. Lord and Bunts reported an increase in ureteral reflux with the duration of paraplegia. They found an increase of 8 per cent in the incidence of reflux over a 5 year period in their experience with paraplegics. Dodson cited an incidence of 12.8 per cent in 854 spinal cord injuries. Edelbrook reported the incidence of reflux in 200 children with hydronephrosis to be 60 per cent. Sixteen per cent of these children died within the first 3 months of life.

ATTEMPTS AT OPERATIVE CORRECTION OF URETERAL REFLUX

The nipple or cuff technique designed to prevent ureteral reflux was first applied by Monod and Van Verts in 1907, and carried further by Gallo, Councill, and Mathisen. Grey and Goodwin summarized the status of this approach in a report of their experience with these procedures in animals. All nipples had disappeared 3 months after operation. Although Councill had originally reported 78 per cent success on short term follow-up, the experience of most investigators has been that the nipples or cuffs had failed to function within a relatively short time after operation.

Hutch (19, 20) recommended lengthening the intravesical ureter thus exposing it to hydrostatic pressure from the distending bladder. He reported an initial success in 78 per cent of cases. Jewett reported that in long-term studies increased back pressure and hydronephrosis occurred in most patients operated on by this technique. The so-called "tunnel" technique described by Leadbetter, Politano, Vest, and Hill are variations of this same principle. Pasquier

summarized the results of this latter approach in a review stating that undesirable complications, such as progressive renal damage or dilatation of the upper urinary tract, occurred relatively frequently even though the reflux had been abolished.

Other investigators, such as Smith and Hinman (39) and Grey and Goodwin have attempted ureteral and ileal intussusception in trying to provide a valve-like function. Hinman (18) was dissatisfied with the ileum thus used as a valve. No long-term results are available on this method. In a recent nationwide survey made by Vinson, Hutch, and Bunts, 169 ureterovesical anastomoses had been performed by all of the methods described with 70 per cent success. This figure compares with a reported 79 per cent success in 83 procedures performed by the Hutch method. No data regarding follow-up time were given.

THE MECHANICAL VALVE

The likelihood of encrustation with urinary salts militated against the use of foreign materials as valves in the urinary tract, but introduction of the inert and so-called "non-wettable" materials such as teflon and silicone seemed to offer a reasonable opportunity for trial of a valve made of these materials. In the valves employed in this study simple hydrostatic principles are used. The major component is a silicone-rubber tube closed at one end and fitted with a small slit at its lateral border. The length of this slit determines the flow capacity of the valve. Thickness of the wall of the tubing and the characteristics of the rubber determine the opening pressure of the valve. The tubing can be encased in several materials. The original valve used in this study was enclosed in stainless steel and had an opening pressure of 8 centimeters of water with a flow capacity of 400 cubic centimeters per 24 hours. Experience in animals suggested that the opening pressure of this valve was too high, and the flow capacity too low. It was modified to produce an opening pressure of 4 centimeters of water pressure and a flow capacity of 1,000 cubic centimeters per 24 hours. The casing of this valve was changed to teflon with 2 flanges for connection or securing the valve in the tissues (Fig. 1.)

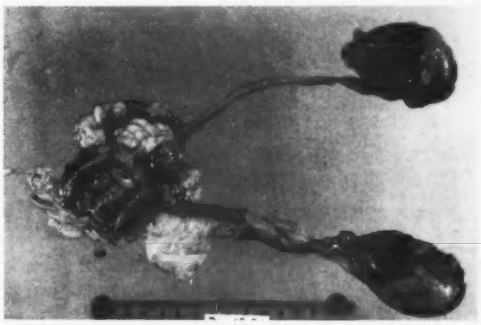

FIG. 2. Autopsy specimen 3½ months after implantation of teflon valve on the right side. The left collecting system is hydronephrotic as a result of inadvertent partial obstruction by suture.

EXPERIMENTAL EVALUATION OF THE VALVE

Adult mongrel dogs were used as experimental animals. First, the stainless steel valves with opening pressure of 8 centimeters of water and flow capacity of 400 cubic centimeters per 24 hours were used in reimplantation of ureters into the bladder. Then, animals were studied similarly using the modified teflon valve with lower opening pressure (4 cm. of water and flow capacity of 1,000 c.c. per 24 hours).

The animals were anesthetized with intravenous pentobarbital, and the peritoneal cavity was opened through a lower midline incision. The ureters were identified and transected approximately 1 inch from the bladder. In the animals in which the ureters were reimplanted with the valve, the stem portion of the valve was inserted into the proximal ureter and tightly secured there with a double ligature of No. 00 silk. The bladder was then incised and the valve inserted so that the bladder wall could be closed between the flanges by means of a purse-string suture. In some animals one ureter was implanted with the other ureter

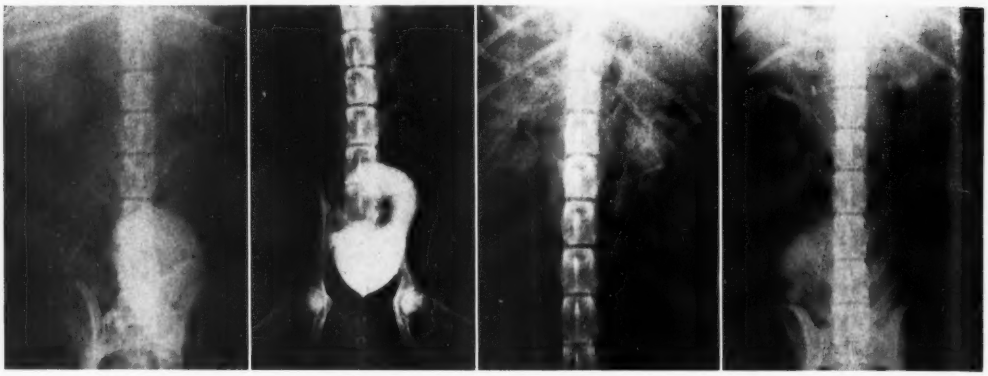

FIG. 3. FIG. 4. FIG. 5. FIG. 6.

FIG. 3. Intravenous urogram 2 months after teflon valve implantation on right side. Note absence of dilatation.

FIG. 4. Postoperative cystogram illustrating absence of ureteral reflux 1 week after teflon valve implantation.

FIG. 5. Typical preoperative urogram.

FIG. 6. Urogram 3 months after teflon valve insertion on right side. Wire rings indicate location of valve. No evidence of urinary stasis.

serving as control while in others one ureter was tightly ligated. In several dogs both ureters were reimplanted into the bladder with the valves.

Intravenous urograms were made preoperatively and at intervals during the postoperative period. Cystography was performed on representative animals in each series. At the time of death or sacrifice of the animals, biopsies were made of the ureteral wall and the tissues surrounding the valve. The ureters and kidneys were removed and examined grossly and histologically for thickening and dilatation.

FIG. 7. Histologic appearance of ureteral wall 1 centimeter from valve 3 months after insertion. Minimal reaction is apparent. ×24.

RESULTS

Group I. The procedure followed in this group consisted of unilateral ureteroneocystostomy using the stainless steel valve (opening pressure 8 cm. water, capacity 400 c.c. per 24 hours). Eight animals were included in this series. All dogs had severe hydronephrosis on the side of valve implantation. It was noted, however, that even after 3 months of uninterrupted use of the valves, there was no evidence of stricture at the ureterovalve or valve-bladder junction. Calculi did not form upon the valve or in the bladder or in the ureter even after the use of a special stasis chamber. There was a remarkable absence of signs of tissue irritation. The animals were sacrificed at intervals of from 1 week to 3 months postoperatively. The conclusions from this part of the experiment were as follows: (1) The valves seemed to be inert in the tissues. (2) Calculi did not form on the valve or in the organs with which it was connected. (3) The opening pressure and flow capacity were inadequate.

Group II. The method in this group was unilateral or bilateral ureteroneocystostomy using the teflon valve (opening pressure 4 cm. of water, capacity 1,000 c.c. per 24 hours). Ten animals were operated upon in this group. The longest survival time was 3½ months (3 animals). The appearance of the urinary tract of 2 of these animals is shown in Figure 2. Two animals were sacrificed 2 months postoperatively and 2 animals 1 month postoperatively. One animal died 7 days postoperatively from urinary extravasation and spreading peritonitis due to a leak at the junction of ureter and valve. One animal died 5 days postoperatively from a wound abscess and septicemia, although the operative procedure appeared to be successful. One animal is alive 6 months after operation and appears healthy with a normal appearing urinary tract on the side operated upon (the right) (Fig. 3). Cystograms show absence of reflux (Fig. 4). Representative urographic appearance is illustrated in Figures 5 and 6.

Specimens from bladder, ureter, and tissues around the valve were taken from the long term survivals for histologic study. As shown in Figure 7 sections of ureter reveal absence of muscular hypertrophy as well as inflammatory reaction. The bladder mucosa was normal throughout. The tissue around the valve consisted mainly of eosinophilic staining collagenous material interspersed with connective tissue. The lower ureter which was tied around the valve neck showed the expected necrosis distal to the ligatures but assumed a normal appearance proximally. Absence of inflammatory changes in the tissues were impressive.

In 1 animal simultaneous cystography and intravenous pyelography 1 week after operation showed prompt dye elimination from both kidneys despite increased intravesical pressure.

One animal at the time of autopsy was found to have severely infected bladder urine and yet had negative urine cultures from the renal pelvis 2 months after implantation of the teflon valve on each side.

SUMMARY

The history of ureteral transplantation is briefly reviewed. The incidence and etiology of ureteral reflux are discussed and operative procedures for correction of ureteral reflux are described. Statistical analysis of the results of these procedures is given and a new approach to the problem of ureteral reflux is developed.

A plastic valve has been used on mongrel female dogs to study the feasibility of correcting ureteral reflux by means of a mechanical valve. Under the conditions of these experiments the following conclusions seem permissible:

1. The teflon valve is nonirritant to the tissues.

2. An opening pressure of 4 centimeters of water and a flow capacity of 1,000 cubic centimeters per 24 hours are adequate for the dog.

3. Ureteral stricture and calculus formation in the urinary tract did not occur.

4. There is absence of ureteral reflux and upper urinary tract dilatation 2 months after insertion of the valve.

5. Retrograde spread of infection is effectively controlled by the valve.

6. The valve functions satisfactorily in the presence of increased intravesical pressure.

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SERUM MUCOPROTEINS IN AFRICAN WOMEN DURING PREGNANCY, THE PUERPERIUM, AND POSTPARTUM

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OUR INTEREST in the serum mucoprotein changes in pregnancy was aroused essentially through our studies of healing cutaneous wounds and arterial injuries. Many investigators have now demonstrated that mucopolysaccharides (M.P.S.) accumulate in the intima of vessels undergoing degenerative changes associated with disease or aging. Some workers like Taylor have suggested that such M.P.S. accumulations in arterial walls are secondary to and even derivatives of the degenerative vascular components. However, there is now a considerable body of evidence to show that intramural M.P.S. accumulations appear early in the pathologic process in arteries. Our own comparisons of the healing of arterial and cutaneous injuries, induced experimentally and occurring spontaneously in man, strongly suggest that the intramural M.P.S. accumulations in injured arteries correspond to a very similar process in cutaneous wounds during the initial stages of healing, prior to collagen formation (9–11, 14). More recently too, information recorded in the literature indicates that degenerative changes, involving M.P.S. accumulations in the walls of arteries, are associated with increases in circulating mucoproteins. Furthermore, our own studies of serum and tissue mucoprotein changes in rats, treated for 5 days only with toxic doses of calciferol, showed a prompt elevation of serum mucoprotein (S.M.P) by the sixth experimental day, when arterial, gastric, and other tissues became heavily laden with both M.P.S. and calcium. Thereafter the S.M.P. of the calciferol-treated rats remained elevated above that of the untreated controls while the acute vascular injuries in the former progressed to sclerosis and stenosis (13, 14, 17). Our own still unpublished data, derived from the study of more than 80 uterine arteries, obtained from Indian and African women of all ages, indicate that profound changes supervene in the connective tissues throughout the body and especially in those of the main uterine artery during pregnancy, between pregnancies and after the menopause (12). Changes in the M.P.S. content of the uterine arteries themselves were especially pronounced in some circumstances which will be described fully elsewhere. Such remodelling of vessels, during pregnancy, with intimal fibrin deposits and even organized luminal thrombus formation, which apparently occurs postpartum, may thus be simply one expression of connective tissue reactions to the profound endocrine changes supervening in pregnancy, immediately postpartum and between pregnancies. We believe that these changes may perhaps also play some part, firstly in "protecting" women from the fatal effects of arterial degenerative change during the active reproductive phases of their lives while, at the same time, perhaps predisposing them to rapid vascular degenerative diseases later in life (10).

In view of all these considerations it seemed worth while to study the S.M.P. changes during pregnancy and the puerperium in an attempt to relate these to the growth of the uterus, placenta, and fetus, and especially to the marked alterations in pelvic, mammary, cutaneous, and other connective tissues known to occur in pregnancy and the puerperium.

Thus, the primary object of this study is

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TABLE I.—SERUM MUCOPROTEIN DURING PREGNANCY, LABOR, AND POSTPARTUM PERIOD

Group	*No. of cases*	*Mean age, years*	*Serum mucoprotein —(mgm. per 100 ml.)— Mean*	±	*S.E.*	*p**
Control	20	26	66	±	3.0	
Pregnancy						.05
13–28 weeks	22	24	80	±	6.1	
29–36 weeks	29	25	75	±	6.6	
36 + weeks	15	30	77	±	5.0	
Labor						
1st stage	26	24	73	±	3.3	
2nd stage	13	22	81	±	5.4	
Postpartum						
0–4 hours	20	25	77	±	3.8	
5–24 hours	29	25	86	±	3.5	.01
25–48 hours	21	26	102	±	6.7	
3–7 days	10	22	134	±	12.6	
8–14 days	9	23	127	±	10.0	.05
15–21 days	6	23	94	±	6.7	

*t-test.

to report the changes in S.M.P. observed by us in 220 determinations on pregnant and parturient African women. Similar studies have been made by several other investigators, notably Shetlar and associates (29, 30), but only in a relatively small number of European women. Secondly, we hope to outline some of the implications of our findings for understanding connective tissue reactions in pregnancy generally, and to assess briefly some of the implications of these findings and those from our own studies of plasma fibrin and fibrinolysins in pregnancy (19) and also during the baboon's menstrual cycle (20), for a fuller appreciation of vascular degenerative diseases in particular. It is hoped thereby, that the possible importance of further studies along these lines may be appreciated and undertaken by others with a view to clarifying the effects of various states of hormonal balance on the connective tissues in general and on those comprising arterial walls in particular.

MATERIAL AND METHODS

Obstetrically normal and healthy pregnant and parturient African women were selected from the antenatal clinic and the labor wards of the King Edward VIII Hospital for the present study. The nonpregnant control group was made up of 20 volunteer African nurses.

Blood collection. Blood samples were taken between 9 and 10 a.m. each day, as diurnal fluctuations in S.M.P. are known to occur. Blood was obtained by "clean" venipuncture with a No. 11 needle, and the serum was removed after centrifuging the blood 1 hour after clotting. Estimations were done after storing in the deepfreeze for up to 2 days; S.M.P. has been shown to be stable at low temperatures.

Chemical methods. S.M.P. was determined according to the turbidimetric micromethod of de la Huerga and associates in which serum is dissolved in 0.85 per cent sodium chloride, and all proteins except S.M.P. are precipitated by addition of 1.8 normal perchloric acid. After filtration through Whatman No. 50 filter paper, the S.M.P. is then precipitated by 5 per cent phosphotungstic acid in 2 normal hydrochloric acid and the turbidity is read at 400 microns with a Zeiss spectrophotometer. Bovine serum albumin (M.P.1) was used for standardization. All estimations were done in duplicate.

OBSERVATIONS

All our data are presented in Table I and Figure 1. From these it will be seen that the mean S.M.P. level rises from 66 milligrams in nonpregnant women to 80 milligrams per 100 milliliters in those studied between the thirteenth and twenty-eighth weeks of pregnancy. Although this seems only a small rise it is nevertheless a significant one ($p<.05$). Thereafter, the levels remained rather constant and only slightly elevated above the levels found in our 20 control African women. With the method here used, we did not encounter in African women the progressive increase in the total S.M.P. described by Shetlar and associates (30) during the last months of pregnancy in European women.

However, we did encounter a notable rise in total S.M.P. within the first 24 hours after labor. This rise was significant ($p<.01$), and it progressed sharply until the seventh day postpartum. The S.M.P. values observed in women studied between the seventh and

twenty-first days after delivery were falling rapidly and progressively. In this regard our findings seem to be comparable with those of Shetlar and associates (30) who also encountered a marked rise during the first 8 days after delivery and a fall thereafter, progressing quite sharply to almost normal levels by the fifty-second day after parturition.

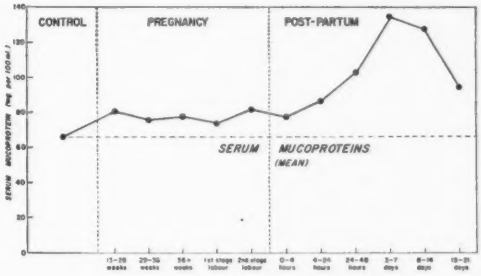

FIG. 1. Mean serum mucoprotein levels in nonpregnant, pregnant, and postpartum patients.

DISCUSSION

Schwartz and Gilmore have recently suggested that low plasma mucoprotein levels in nomadic Australian aborigines may be of significance in explaining the low incidence of atheroma among these people. Whatever the implications, it seems of interest to note that the total S.M.P. in our 20 nonpregnant African women (66 mgm. ± 3.0) were lower than the values for normal European subjects reported by Schwartz and Gilmore (95.6 ± 2.81) and especially by Stary. The latter author stipulated 110 milligrams per 100 milliliters as the value for "normal" adults while de la Huerga and associates, whose methods were used in our study, reported 77.1 ± 1.4 milligrams per 100 milliliters as the normal value in women.

Apart from this, our findings regarding the S.M.P. changes during pregnancy and parturition in African women conform for the most part with those already reported by other workers who, using other methods, have studied serum polysaccharides in pregnant women of a different race and socioeconomic status.

Shetlar and associates (29), from a comparison of serum glycoprotein, seromucoid, and C-reactive protein changes suggested that "... the elevated serum protein levels of pregnancy may be due to causes other than inflammation." Data from the literature and from our own studies in rats and baboons seem to substantiate this opinion.

We would like to go further, however, and suggest that the slightly elevated S.M.P. levels during pregnancy and the marked rise, particularly during the first week post partum, are simply one expression of the depolymerization of the connective ground substances which occur, probably throughout the body, but certainly in the genital tract in pregnancy and especially during the involutionary changes in the uterus and other genital connective tissues immediately post partum. In support of this suggestion we adduce the following facts. For example, it is known that, in animals and man, the S.M.P. become markedly elevated following parathyroid injections. Thus Engel and Bloomfield and Hayes stated that this increase in S.M.P. occurs *pari passu* with depolymerization of connective tissue components, at least in bone and skin. Harkness and Harkness (23) and Harkness (22), on the other hand, have shown that the rat's uterus loses large amounts of collagen during the first few days after delivery and that this is associated with an increase in uterine hexosamine content. Perl and Catchpole have also reported the occurrence of considerable depolymerization of perisymphysial connective tissues in relaxin-treated guinea pigs, but unfortunately they did not examine the associated S.M.P. changes. The increase in S.M.P., reported by Spicer and Bryant in papain-treated rabbits, from whose cartilage ground substances M.P.S. are being actively mobilized, also seems to substantiate this possibility. While this work was in progress we received the report of Schwartz and Gilmore who also thought that the elevated S.M.P. and hexosamine levels described by them in atherosclerotic subjects were attributable to depolymerization

of arterial connective tissue ground substance.

Furthermore, our studies during the menstrual cycle in baboons have shown a progressive increase in the S.M.P. levels during the perineal turgescence in the first part of the cycle. This plasma component rises even further and very sharply until 1 week after deturgescence has been initiated in the immediately postovulatory period of the cycle. This evidence clearly suggests that the S.M.P. levels become increased during the synthesis of the mucoprotein-rich perineal tissue, possibly where available circulating materials are being used. Yet the S.M.P. levels rise to even greater values during the early stage of deturgescence of the sex skin —a process which in all probability involves depolymerization of the connective tissue ground substance within the already turgescent perineum.

Schwartz and Gilmore have summarized some of the evidence to show that depolymerization of connective tissue ground substance, induced by hyaluronidase injections, is accompanied (or followed) by increase in S.M.P. However, it is relevant to mention that S.M.P. may also be raised during active synthesis of tissue constituents, for Boas and Peterman showed that S.M.P. is higher in young actively growing than in older rats, while Schjeide and Ragan disclosed a progressive increase in S.M.P. in chicks until they hatch and even for some time thereafter. The rising S.M.P. during perineal turgescence in the baboon may perhaps reflect extremely active elaboration of this plasma component, perhaps by the liver, which is, nevertheless, being rapidly removed from the blood for perineal synthesis at this time of the cycle. The even greater elevation in the first week of deturgescence, however, may reflect a maintained extraperineal synthesis together with decreased perineal utilization at this time, or alternately, greater synthesis plus active depolymerization and mobilization of previously formed perineal ground substance. On this basis, the slight elevations, especially in early pregnancy, may be merely one expression of increased maternal synthesis of essential materials for use by the actively growing embryo. The sharp rise shortly after delivery, however, may, as suggested for the baboon, reflect either maintained maternal synthesis or, as we believe, active M.P.S. mobilization from genital connective tissues during their most active phase of postpartum involution. The sharp drop at 15 to 21 days may, in turn, indicate renewed use of mucoprotein—this time for milk secretion. The report by Harkness and Harkness of very rapid collagen mobilization from the rat's uterus within the first 4 days of parturition would seem to support our explanation of the postpartum S.M.P. rise in African women. These considerations certainly seem to delineate several excellent uses for radioactive tracer studies in pregnancy and parturition.

All this evidence thus seems to indicate the association of elevated S.M.P. with those connective tissue reactions involving either the rapid accumulation of M.P.S. or sudden mobilization. Viewed in this light it seems possible that the oft-described acute increase in S.M.P. following operative trauma, stress, or treatment with ACTH may be a reflection, not so much of inflammation itself, but rather of those specific aspects of inflammation which contribute toward repair. For, the M.P.S. content of chick embryos and of healing wounds is known to increase suddenly prior to collagen synthesis and to decrease with the progressive deposition of collagen. Moreover, many of the stimuli just enumerated are known to induce the rapid mobilization of polysaccharides from mast cells as well.

As for the hormonal factors which may influence the connective tissues, it seems, from the analysis just given, that the connective tissues are particularly sensitive to at least the following groups of hormones, namely: pituitary, somatrophic hormone, parathormone, thyroid and adrenocortical hormones, and finally, relaxin, especially in estrogen-primed animals. Although some tissues seem much more sensitive to particu-

lar hormones, it is nevertheless a truism that all tissues are responsive, in one or other degree, to all hormones. Consequently, it is not surprising to find that purplish cutaneous striae, indistinguishable from the classical striae gravidarum, are common in Cushing's disease, whether of pituitary or adrenal origin. Moreover, our preliminary histochemical studies of striae gravidarum, in different stages of their development, reveal distinct localized accumulations of sulfated M.P.S. in the stratum papillare of the dermis. This is taken to indicate that profound changes are occurring in the dermal connective tissue ground substance prior to the appearance of the striae themselves. Perhaps the added intra-abdominal tension, late in pregnancy, may simply be the final force precipitating the striae in connective tissues whose tensile strength is already decreased; for it was shown by Herrick in 1945 that the tensile strength of connective tissues can be profoundly altered by the actions of hormones. We regard the macroscopically and microscopically detectable alterations in the skin, during pregnancy, as merely one aspect of the over-all changes in connective tissues throughout the body. The similarity between the striae of pregnancy and those in Cushing's disease and the fact that the latter is known to be a result, at least in part, of adrenal hyperactivity suggest that this endocrine gland may also be playing a considerable role, in concert with estrogen and relaxin, in modifying the connective tissues during pregnancy. Other evidence in support of this possibility has been adduced elsewhere and is apparent also from the increased plasma cortisone levels and increased ketosteroid excretion known to be present during pregnancy.

It may be significant, too, that the S.M.P. levels are elevated in diabetics with arterial degeneration, especially since there is considerable evidence that the active progress of atheromatous and other arterial degenerative changes are associated with considerable increases of M.P.S. in the areas of damage in affected arteries. Moreover, it has been shown by Buck (3) and Buck and Heagy (4) in cholesterol-fed rabbits, and by Noble and associates in man, that such M.P.S. accumulations within arterial walls precede the deposition of lipids. We have suggested elsewhere (9–11, 14–18) that the M.P.S.'s which accumulate in the walls of injured arteries, as they grow or undergo repair may also play an important role in the localized binding of circulating lipids. This opinion is further substantiated by the close relation shown by Faber to exist between quantitatively determined increases in arterial M.P.S. and cholesterosis of these arteries. His findings were subsequently confirmed histochemically by Bunting and Bunting and by our own more recent histochemical studies of growth, regeneration, repair, and degeneration of human arteries. The data of Schwartz and Gilmore also support this interpretation of available data as do the changes seen by us in the uterine arteries during pregnancy, between pregnancies, and after the menopause.

The hormonally mediated changes in the serum mucoprotein and the M.P.S. content of many connective tissues, and perhaps especially of arteries, evinced in pregnancy, and during the menstrual cycle in the baboon, indicate the greater sensitivity of these structures to certain hormonal influences.

That remodelling of arterial and other connective tissues during pregnancy may "protect" the arteries of women from degenerative changes during the reproductive period, while perhaps predisposing them to rapid deterioration shortly after the menopause, is also suggested by several available facts. For, Wuest, Dry, and Edwards have shown the incidence of coronary atherosclerosis to be 10 to 45 per cent greater in bilaterally oophorectomized than in control women. Their data also reveal the sharp increase in the incidence of coronary arterial degenerations in women shortly after the menopause, as the incidence of coronary lesions increases from approximately 20 per cent in women aged 50 to 59 years to almost 60 per cent in 70 to 79 year old women.

Griffiths has also drawn attention to many aspects of the "extragenital" actions of the ovaries. Besides, we have shown elsewhere, in the same series of cases as presented here, that the plasma fibrinolytic activity decrases during pregnancy and returns to control levels within 24 hours of delivery (19). This postpartum rise in plasma fibrinolytic activity has now been demonstrated by us to be associated with a significant *decrease* in plasma antifibrinolysin. Moreover, the fact shown by us (15) that rats which have had several litters later in life develop severe arterial lesions far more frequently than virgins of the same age suggests that the active vascular remodelling which seems to occur during pregnancy may predispose the arteries of the breeding females either to naturally occurring or to experimentally induced degenerative changes later in life. The endocrine changes accompanying pregnancy and the puerperium, as assessed from these alterations in blood, may induce their effects on both plasma and connective tissues through several different mechanisms. These findings indicate several new avenues for investigating connective tissue changes with aging and degenerative diseases.

SUMMARY

1. The serum mucoprotein (S.M.P.) changes based on 220 determinations in control, pregnant, and parturient women are recorded. It is shown that a significant increase in S.M.P. occurs by the second trimester and that this is maintained throughout pregnancy.

2. The S.M.P. rises rapidly during the first 7 days after delivery and declines quite quickly during the ensuing 2 weeks.

3. Critical assessment of these findings in the light of available literature and other experimental data from this laboratory indicates that elevations of S.M.P. may be a reflection of either rapid synthesis by, or sudden mobilization of mucopolysaccharides (M.P.S.) from connective tissues throughout the body and possibly in some circumstances particularly from arteries.

4. Some possible implications of these findings for an appreciation of the synthetic, catabolic, and degenerative processes in genital and arterial connective tissues throughout the body, especially during pregnancy and the puerperium, are briefly outlined.

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THE EFFECT OF RECURRENT BOUTS OF PANCREATITIS ON PANCREATIC FUNCTION

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LITTLE IS KNOWN about the function of the pancreas of a patient surviving 1 or more attacks of acute pancreatitis. Dreiling has reported the results of secretin duodenal drainage tests in 48 patients following 1 attack of acute pancreatitis. Seventy-three per cent of these patients had normal values for bicarbonate concentration and total amylase (units/kgm.) while 77 per cent had normal volume responses.

It has been suggested that pancreatic function is impaired early in the disease necessitating early surgical intervention to prevent progression of the process. The destruction of acinar tissue by 1 or more exacerbations of pancreatitis could possibly lead to diminution of output of the enzymes, amylase and lipase, and thus make serum values in future attacks poor guides to diagnosis. Finally, the amount of impairment of external pancreatic secretion becomes important as a possible prognostic sign for physician and patient. This study was undertaken to evaluate the exocrine function by means of a secretin duodenal drainage test in patients who experienced 1 or more bouts of acute pancreatitis.

METHOD AND MATERIAL

The diagnosis of acute pancreatitis in this study was made exclusively by one of the authors. It was made in a "forward" and a "backward" way in each instance. The former consisted of deciding during the acute illness that the case was one of acute pancreatitis on the basis of appropriate history, physical signs, and laboratory data (all patients had elevated amylase values). In 2 instances exploratory laparotomy revealed acute hemorrhagic pancreatitis. Otherwise, all patients were treated conservatively, and upon recovery, a backward diagnosis was made upon the report of a normal gallbladder and gastrointestinal series. Four patients with acute pancreatitis associated with acute cholecystitis underwent exploratory procedures 7 to 30 days after admission, and the diagnosis of pancreatitis was established by an enlarged firm head of the pancreas or by fat necrosis.

The secretin duodenal drainage test has been previously described. Briefly, it consists of the passage of a double lumen Einhorn tube under fluoroscopic control to rest in the third portion of the duodenum just proximal to the ligament of Treitz. One clinical unit of secretin per kilogram of body weight is given intravenously, and duodenal contents are collected for 80 minutes. The specimen is analyzed for volume produced, maximum bicarbonate concentration, and amount and concentration of enzyme, notably amylase.

RESULTS

Nineteen secretin tests performed on these patients (excluding the acute hemorrhagic variety) have been classified as: A—associated with alcoholism, 11 cases; B—associated with gallbladder disease, 4 cases; C—cause unknown, 4 cases. The results are summarized in Table I.

There are no significant differences between these groups except that group C had a somewhat higher mean bicarbonate value

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TABLE I.—RESULTS

Patient	*Class.*	*No. of attacks*	*HCO_3 (conc. 60 mins., mEq./l.)*	*Amylase total in 20–80 mins.*	*Kgm.*	*Amylase/kgm.*	*Months after first attack*
1	A	1	68.9	368.5	60	6.14	.5
2	A	1	175.5	503.8	55	9.24	.3
3	A	3	5.7	359.0	61.8	5.81	24.0
4	A	1	6.1	229.5	91	2.52	16.0
5	A	4	89.8	190.0	70	2.71	36.0
6	C	1	237.0	512.5	76	6.74	.7
7	C	1	203.6	316.2	57	5.55	.3
8	A	2	144.6	429.0	93.6	4.58	9.0
9	C	1	185.0	362.0	91	3.97	29.0
10	A	5	122.0	382.0	52.7	7.25	48.0
11	B	8	112.0	548.2	85.9	6.38	60.0
12	A	3	85.4	677.4	90	7.53	12.0
13	A	1	222.3	164.0	86.4	1.90	12.0
14	A	2	96.3	598.6	77	7.77	12.0
15	B	1	131.0	513.2	70	7.33	.3
16	B	1	102.0	484.0	63.6	7.61	.5
17	B	1	144.4	376.0	67.4	5.57	.5
18	A	3	112.0	621.6	63.8	9.74	14.0
19	C	1	138.6	508.0	72.4	7.02	.2
					72.9		
					±13.4		

TABLE II.—RESPONSE TO SECRETIN TEST

Variable	*Amylase, mgm./hr./kgm.*		*HCO_3, mEq./hr.*	
	Regression slope	*T-statistic*	*Regression slope*	*T-statistic*
No. of attacks	+.108	1.63	—9.12	—4.9
Duration	—.0057	— .78	—2.45	—8.09
For 17 d.f.	(At 95 per cent c.l.)	±1.74	(At 99.75 per cent c.l.)	±3.22

than the others. This may be the result of each patient in the group having had only a single attack.

These data may be compared with the responses of 10 "normal" volunteers to the same procedure (2). It can be shown by application of the T-test that each of the various bicarbonate parameters shows dependence upon the others; and similarly for the various estimates of amylase activity. On the other hand, this same T-test shows clearly that in this series of apparently normal persons, the chosen estimates of bicarbonate and amylase vary independently of one another.

In the normal series the mean of amylase per kilogram less its standard deviation is: 8.74—2.92 = 5.82; 8 of 19 of the pancreatitis values (41.7 per cent) lie below this, and none above. We are thus obviously dealing with depressed function as judged by this criterion. The bicarbonate values of the pancreatitis group show that 9 values (42.2 per cent) lie below the normal mean minus its standard deviation, while 3 (15.8 per cent) lie above the mean plus 1 standard deviation, from which a similar conclusion may be drawn. Thus, in the cases of pancreatitis generally, there appears to be a group of patients whose pancreatic function, judged by 2 independently varying criteria, is significantly depressed, although in any given instance this may or may not be true of either criterion.

It has often been stated that, with each repeated attack of pancreatitis, or with the passage of time during the disease, pancreatic function progressively decreases. From Table I, the data have been analyzed to see whether or not they support such a contention.

Relationships such as these, if true, are easily visualized in scattergrams, such as Figures 1 and 2, in which the duodenal amylase (as mgm./hr./kgm. of body weight) is plotted, first against the duration of disease since first onset, and then against the number of attacks sustained. From inspection one would intuitively say that the present data show no dependency. If one cal-

TABLE III.—ACUTE HEMORRHAGIC PANCREATITIS

Patient	*Class.*	*No. of attacks*	*HCO_3 (conc. 60 min., mEq./l.)*	*Amylase total in 20–80 mins.*	*Kgm.*	*Amylase/kgm.*	*Mos. after first attack*
1	A	1	51.9	231.8	64.5	3.59	1.5
2	A	1	138.7	20.4	92.3	0.22	4.0
3	A	1	54.1	71.0	81.8	0.87	1.3
3*	A	1	92.2	268.4	81.8	3.28	16.0
2*	A	1	124.2	308.0	96.0	3.21	13.0

*Follow-ups.

culates the "regression line" of this relationship, its slope appears to differ only negligibly from zero, confirming this impression.

There is, moreover, a method of some elegance available by which we may test our hypothesis of nondependency, i.e., that B, the slope of the line, is not significantly different from zero. This T-test, numerically summarized in Table II clearly shows that at least 19 times out of 20, the slope of the regression line might have at least this much divergence from zero, by chance alone, thus failing to show significant dependence.

The response of the duodenal bicarbonate concentration to secretin, on the other hand (measured as mEq./l. in the first 20 minutes of the test), when plotted in the same way in Figures 3 and 4, may or may not show dependence. The calculated regression lines show a clear-cut downward trend, one which may be significant. Application of the T-test to these data indicates that, even at the 99.75 per cent confidence level, one must reject the hypothesis that $B=0$; in other words, that there is a very high probability that the data indicate functional loss of pancreatic tissue with repeated attacks and with passing time—at least as judged by the bicarbonate response.

The amylase response gave no such indication—in fact it was shown to be independent of these parameters. What is the implication of the apparent discrepancy? If it be true, as has often been said, that secretin calls forth a maximal "effort" on the part of the pancreas to produce bicarbonate, but fails specifically to stimulate maximal production of amylase, the observations make some sense. The partly damaged, incompletely recovered pancreas with each successive attack loses a portion of its maximal response capacity (so far as bicarbonate is concerned), but continues to put out respectable amounts of amylase (for which, after all, the stimulus has made no particular demand). If this were so, then in the present series there should be no correlation between the two responses, amylase and bicarbonate, any more than there is in the normal individuals. That this is indeed so is demonstrated by the fact that the T-test will not allow one to reject the hypothesis that they are independent.

Table III presents 5 other observations, all in patients with proved severe hemorrhagic pancreatitis. Three observations were made shortly after the acute phase, and the rest are follow-ups of 2 of these. With so few cases to deal with, there is no point in statistical analysis. The data do show clearly, however, that the seriously damaged gland may have marked depression of its capacity to produce both bicarbonate concentration and amylase; but that, in a 1 to 1½ year period, it is capable of a remarkable return of function in both regards.

DISCUSSION

Recurrent bouts of interstitial pancreatitis affect the response of the pancreas to secretin by diminishing the bicarbonate values progressively with successive attacks. Enzyme values represented by amylase in these studies remain relatively unimpaired. Since secretin brings about the production of pancreatic juice high in water and bicarbonate and low in enzymes, the continued downward trend of bicarbonate production with the increased number of attacks becomes significant.

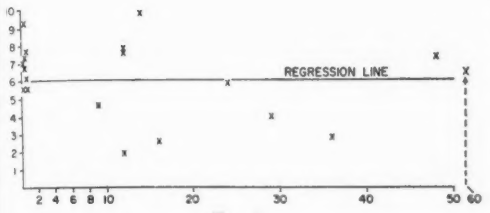

FIG. 1.

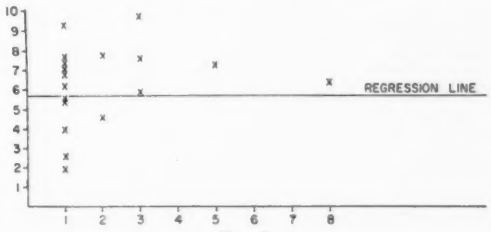

FIG. 2.

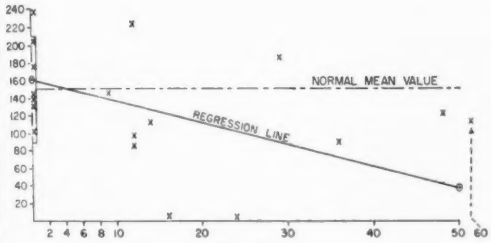

FIG. 3.

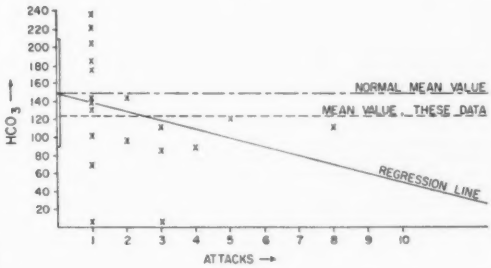

FIG. 4.

FIG. 1. Duodenal amylase (mgm./hr./kgm. of body weight) plotted against duration (mos.) of disease since first onset.

FIG. 2. Duodenal amylase (mgm./hr./kgm. of body weight) plotted against number of attacks.

FIG. 3. Duodenal bicarbonate (mEq./l.) plotted against duration (mos.) of disease since first onset.

FIG. 4. Duodenal bicarbonate (mEq./l.) plotted against number of attacks.

It is true that one should not wait until the triad of calcification of the pancreas, steatorrhea, and diabetes is present before the diagnosis of chronic pancreatitis is made. On the other hand, more than one attack of acute pancreatitis should not lead to the conclusion that chronic pancreatitis is present. Chronicity implies pancreatic dysfunction of a permanent, unremitting nature with little hope of improvement. Two patients with acute hemorrhagic pancreatitis showed remarkable ability to recover in their response to secretin in a little over 1 year from the initial test. The presence of an impaired secretin duodenal drainage test on 1 occasion following an acute attack of pancreatitis does not necessarily indicate a chronic state of pancreatic insufficiency or the inability of the gland to recover.

Until such time as pancreatic function becomes permanently impaired, this type of patient should be considered as a case of recurrent pancreatitis. This differentiation is stressed because of therapeutic implications. It has been stated that pancreatic function is impaired early in pancreatitis necessitating prompt surgical intervention. The present data do not bear out this concept. The authors believe that patients with acute recurrent pancreatitis and many with chronic pancreatitis are best managed by a medical regimen, surgery being reserved for the following: (1) uncontrollable pain, (2) biliary tract disease, (3) jaundice, (4) pseudocyst, and (5) to rule out carcinoma or definitely establish a doubtful diagnosis. The slowness with which pancreatic impairment occurs as the result of multiple attacks of recurrent pancreatitis and the remarkable ability of the pancreas to recover from a marked insufficiency contraindicate surgical intervention for the reason of improvement of function alone.

Amylase values in the pancreatic juice show no definite downward trend in this group of patients. In chronic pancreatitis

these values should be depressed. Thus, the patient with acute recurrent pancreatitis has the ability to sustain an elevation of serum amylase during an attack, whereas the patient with true chronic pancreatitis may not produce enough enzyme to allow a rise in the serum. This has been pointed out many times in the past but is only reinforced here further to differentiate the two groups of patients.

SUMMARY

1. Pancreatic function in response to secretin tends to decrease in a linear manner with progressive attacks of the disease as reflected in bicarbonate values.

2. No individual patient, however, should be labelled as having chronic pancreatitis unless the function of the pancreas is markedly impaired in a permanent way for both bicarbonate and amylase and correlated with clinical history and stage of disease.

3. Patients with repeated episodes of pancreatitis are best referred to as acute recurrent, with an expected progressive impairment of bicarbonate excretion after each attack. The point at which the individual case is irretrievable as far as functional response to secretin is concerned cannot be stated.

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NORMOTHERMIC PERFUSION AND REPLANTATION OF THE EXCISED DOG KIDNEY

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STUDIES of hypothermic, whole blood perfusion of the excised dog kidney have revealed that pump-oxygenator-kidney preparations, without passage of the perfusate through animal lungs, maintained urine production for periods of about 7 hours (2). In agreement with the findings of earlier investigators, these preparations were notable for their subnormal blood flow values.

The present study was formulated to assess the influence of normal temperature, the effect of reducing the percentage of blood volume removed from the blood donor animals, and the viability of such perfused kidneys after replantation to the original host.

This report deals with two experimental series: group I, normothermic whole blood perfusion of the excised dog kidney (14 preparations); group II, normothermic perfusion followed by kidney replantation (9 preparations).

METHODS

The apparatus and general methods of perfusion were identical with those described in the previous article (2), except that the temperature of the perfusate and kidney chamber was constant at 38 degrees C. (rather than 25 degrees C.). The apparatus consisted of tygon tubing, siliconized glass vessels, and a pulsatile finger-cot pump. The kidney was placed in a sealed, constant temperature chamber. Arterial blood pressure was maintained at 120 to 140 millimeters of mercury. Oxygenation by falling film diffusion, as employed in the experiments, achieved arterial oxygen saturation ranging between 80 and 90 per cent.

When replantation was to follow perfusion, the apparatus was sterilized by circulation of 600 milliliters of sterile isotonic saline, 600,000 units of penicillin, and 1 gram of streptomycin for 1 hour on the day prior to, and on the day of the experiment. The plastic arterial, venous, and ureteral cannulas were immersed in sterilizing solution for 12 hours.

Operative methods. Unselected mongrel dogs in apparent good health were used. For the perfusions of group I (normothermic whole blood; no replantation), the kidney was excised under pentothal sodium anesthesia (30 mgm. per kgm.); perfusion was started within 20 minutes of interrupting the blood supply.

For the experiments of group II (normothermic perfusion followed by replantation), pentobarbital sodium (30 mgm. per kgm.) was used. The left kidney was excised through a midline abdominal incision; perfusion was begun within 20 minutes and was continued for 3 hours. Upon completing perfusion, the kidney was immersed in penicillin-streptomycin solution and replanted in the donor's right iliac fossa by a technique described elsewhere (4). Since the length of the latter procedure was about 50 minutes, the total ischemic interval was 70 minutes. Six

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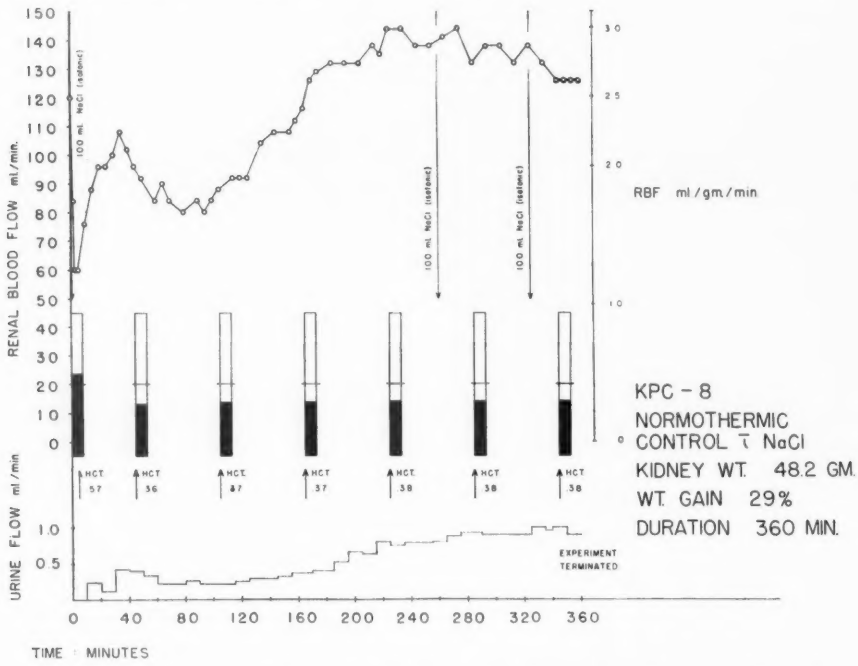

FIG. 1. Perfusion experiment from group Ib. From above down, plots indicate renal blood flow, hematocrit, and urine flow. Additions of saline at 250 and 320 minutes. Note sharp initial decrease of renal blood flow, followed by slow rise.

hundred milliliters of isontonic saline were given intravenously to the subject animal at the close of the procedure. No anesthetic was given between the nephrectomy and replantation. Only 9 to 15 milligrams of pentothal sodium were necessary for anesthesia during the replantation.

The remaining, normal kidney of each donor was resected at 3 to 4 weeks after replantation with 1 exception, in which instance a bilateral nephrectomy was performed at the time of perfusion (1 animal of group IIb). All animals were thus ultimately dependent upon a solitary perfused kidney.

All dogs undergoing replantation received 300,000 units of procaine penicillin and ½ gram of streptomycin intramuscularly daily for 10 days. Urine collection by catheter was avoided because of the high risk of infection. The animals were maintained on a meat diet and daily exercise.

Chemical analyses. For experiments of group I, urine and plasma concentrations of sodium and potassium were determined on a Baird Associates internal standard flame spectrophotometer, total solute concentrations were determined by freezing-point depression in a Fiske osmometer, and creatinine levels were measured by the Jaffe reaction and colorimetry.

TABLE I.—PERFUSION OF EXCISED KIDNEY AT 38 DEGREES C.

Group	*No. of preparations*	*Perfusate (whole blood)*	*Dog weight, kgm.*	*Diluents*
Ia	7*	600 ml. autol. 600 ml. homol.	14–18	Isotonic saline; 5 per cent dextrose in water
Ib	5	600 ml. homol.	22–25	Isotonic saline
Ic	2	300 ml. homol. from each of 2 dogs. Total: 600 ml.	20	Locke's solution with creatinine

*Two preparations discarded because of critically low blood flow.

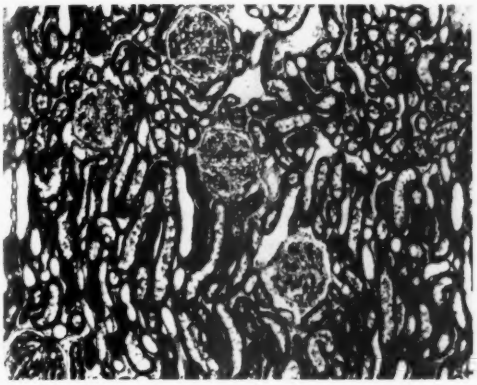

FIG. 2. Photomicrograph of group Ic kidney; perfusion with homologous blood from 2 donors (300 ml. from each). Note patency of tubular lumens and slight interstitial edema. Hematoxylin and eosin, ×63.

EXPERIMENTAL GROUPS

Group I. The 14 perfusion preparations are subdivided into 3 groups (Table I).

In group Ia (7 preparations) the perfusate was 600 milliliters of fresh, heparinized (80 mgm. sodium heparin per 500 ml. blood) autologous blood and 600 milliliters of fresh, heparinized homologous blood from dogs weighing 14 to 18 kilograms. Early in the perfusion, isonatronic sodium chloride solution was added to the perfusate in quantity sufficient to place the hematocrit in the 35 to 45 range.

Two of the 7 experiments were discarded because of critically low blood flow. The remaining 5 preparations were arbitrarily terminated after 300 to 400 minutes, in the presence of satisfactory renal blood flow.

In group Ib (5 preparations) a smaller percentage of total blood volume was removed from the blood donor animals (600 ml. from dogs weighing 20 to 25 kgm.).

In group Ic (2 preparations) the perfusate was comprised of 300 milliliters of homologous blood from each of 2 donors (total 600 ml.). Creatinine clearance measurements were made after the addition of Locke's solution with creatinine (250 mgm. creatinine per 100 ml. Locke's solution), infused at a rate one-tenth the estimated renal plasma flow, thereby producing a plasma

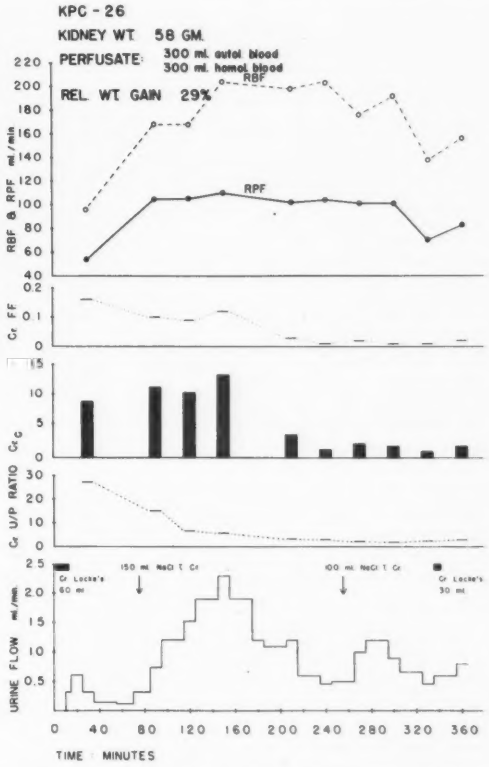

FIG. 3. Pattern of creatinine clearance and urine-plasma concentration ratio under saline diuresis in a group Ic experiment. From above down, renal blood flow, renal plasma flow, creatinine filtration fraction, creatinine clearance, creatinine urine-plasma concentration ratio, and urine flow. Note slow decline of creatinine urine-plasma concentration ratio toward unity.

concentration of about 25 milligrams per 100 milliliters. Isonatronic saline-creatinine solution (25 mgm. creatinine per 100 ml.) was added twice during each perfusion. The duration of perfusion was 360 minutes in both cases. The changes in creatinine clearance and filtration fraction were observed in correlation with the saline-induced changes of plasma flow.

Group II. The 9 preparations of group II are subdivided into 3 groups. In all experiments replantation followed perfusion (Table II).

In group IIa, kidneys were perfused for 3 hours by the pump-oxygenator, using

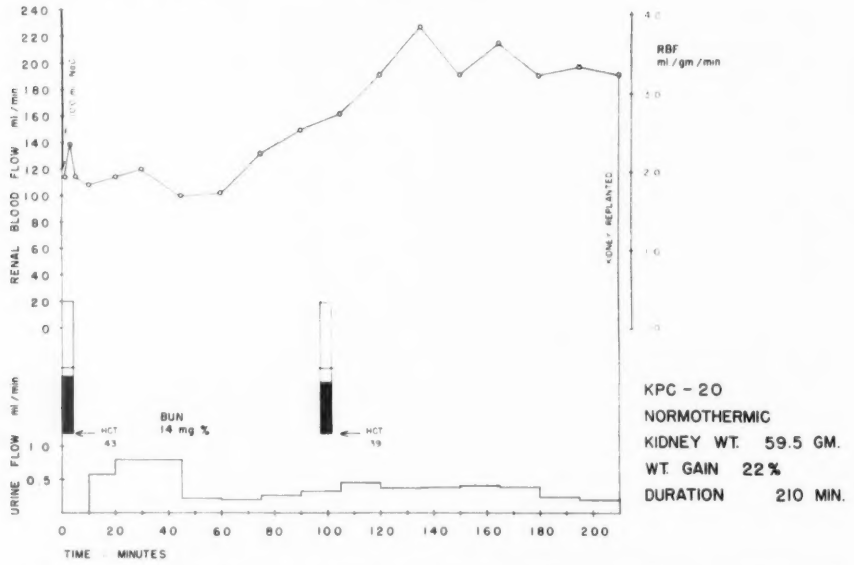

FIG. 4. Protocol chart of group IIa (mixed homologous blood) perfusion. Note absence of initial decrease of blood flow, and sustained normal flow present at time of replant.

mixed homologous blood. Not more than 300 milliliters of blood were withdrawn from any one of the donors.

The kidneys in group IIb were placed in the constant temperature chamber and perfused by intact homologous dogs (in place of the pump-oxygenator), using plastic cannulas to link the femoral arteries and veins to the renal vessels. No additional blood was added to the system.

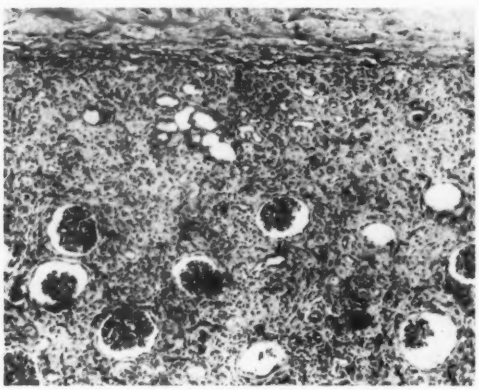

FIG. 5. Photomicrograph of replant kidney from group IIa (mixed homologous blood) 3½ weeks after perfusion-replant. The capsule is thickened and contains dense collagen. Glomeruli are normal. Few tubular lumens are identifiable. Interstitial edema is marked. Hematoxylin and eosin, ×69.

In group IIc, the kidneys were perfused by the pump-oxygenator, using 600 milliliters of autologous blood. The blood-kidney donor animal was transfused with an equal quantity of homologous blood.

RESULTS

Group I. In Figure 1 is depicted a typical preparation from group Ib, illustrating the capacity of such preparations for maintaining renal blood flow between 2.5 and 3.0 milliliters per gram of kidney per minute. The course of the preparations in group Ia was similar, except that the average blood flow was in the range of 1.0 to 2.5 milliliters per gram of kidney per minute. In both groups, there was a sharp initial drop of blood flow—about 75 per cent in group Ia and 50 per cent in group Ib. The rise to maximal flow required an average of 180 minutes in both groups.

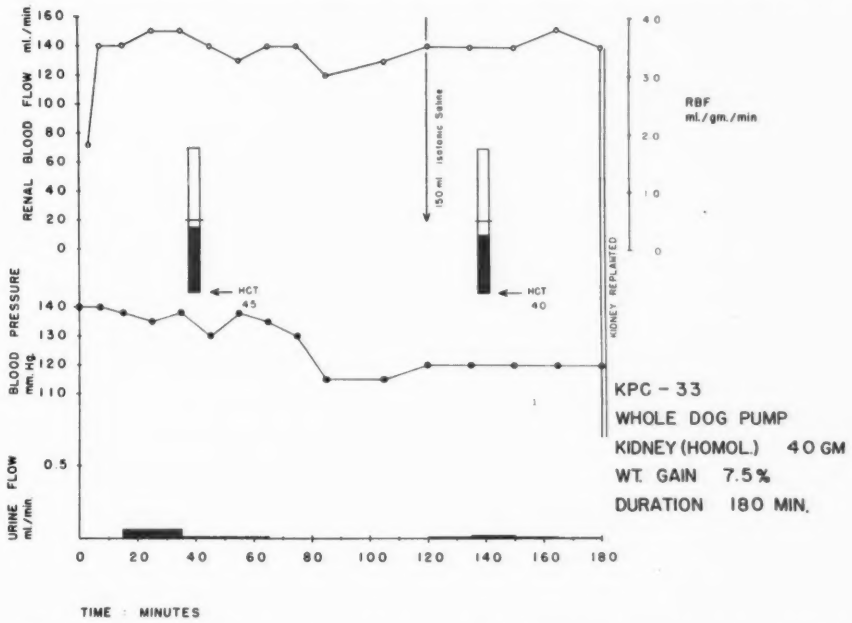

FIG. 6. Course of perfusion from group IIb (intact dog as pump). Note good level of renal blood flow and paucity of urine output.

The pattern of urine production was similar in the two groups, urine flow beginning within the first 15 to 20 minutes and ranging between 0.5 and 1.0 milliliter per minute.

The kidneys of group Ia gained weight over a range of 30 to 40 per cent, while those of group Ib gained 25 to 35 per cent.

In the 3 preparations of group Ib, there was a progressive rise of serum sodium concentration, a fall in potassium concentration, and persistent elevation above normal of total solute concentration.

The two kidneys of group Ic doubled the renal plasma and blood flow in the first 2 hours, while the creatinine clearance rose by 50 per cent. Figure 3 depicts the course of 1 of these preparations.

Histologically, there was minimal evidence of anatomic distortion. In Figure 2 appears a photomicrograph from a kidney of group Ib. The renal tubules appeared normal, except for slight swelling of occasional tubular cells and slight interstitial edema. The glomeruli and blood vessels did not appear abnormal.

Group II. During perfusion the kidneys of group IIa (see Table II) followed courses of blood and urine flow similar to those of groups Ia and Ib. The mean renal blood

TABLE II.—PERFUSION OF EXCISED KIDNEY AT 38 DEGREES C. FOLLOWED BY REPLANTATION TO ORIGINAL HOST

Group	*No. of preparations*	*Perfusate (whole blood)*	*Result after replant**
IIa	3	300 ml. homol. from each of 2 dogs	All animals died in uremia after removal of normal kidney; ? rejection
IIb	3	Homologous; intact dog as pump	All recipient animals alive and well after removal of normal kidney
IIc	3	600 ml. autol. blood; kidney donor transfused with 600 ml. homol. blood	1 kidney: thrombosis of replant artery (technical failure); dog died 1 animal died of cardiac arrest; replant normal 1 animal now alive and well after resection of normal kidney

*All normal kidneys were removed 3 to 4 weeks after perfusion-replant, with the exception of 1 animal in IIb in which both kidneys were removed at the time of perfusion.

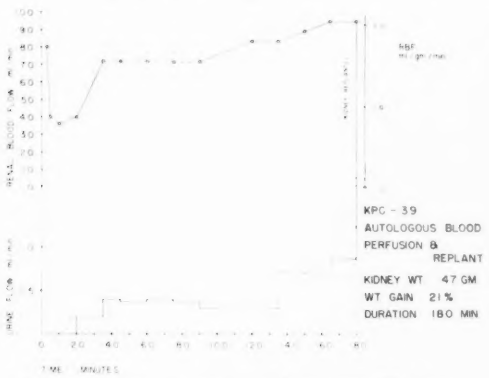

FIG. 7. Course of experiment from group IIc (pump-oxygenator perfusion with autologous blood).

flow in all 3 experiments of this group fell between 3.0 and 4.0 milliliters per gram of kidney per minute (Fig. 4). Although the dogs were normally active from the day of replantation, the replanted kidney became palpably enlarged by the fifth postreplant day and continued to expand. All animals became uremic after removal of the normal nonperfused kidney (4 weeks after perfusion-replantation) and died on the third post-nephrectomy day. In all cases, the arterial, venous, and ureteral anastomoses were patent at necropsy, but subcapsular necrosis was grossly apparent with obliteration of the normal cortimedullary architecture.

Histologically, there were scattered areas of tubular dilatation, with flattening of epithelium in some regions and thickening in others. There was moderate interstitial edema and occasionally large calcium deposits in tubules. There were no periglomerular or perivascular cell infiltrations (Fig. 5).

In group IIb the average total ischemic interval was 70 minutes; the average weight gain was 6 per cent. Figure 6 describes a typical experiment from this group. It is noteworthy that the maximum renal blood flow was reached within the first 10 minutes of perfusion and that very little urine was produced.

Each animal of this group survived removal of the nonperfused kidney and subsisted on the single perfused kidney. One animal actually subsisted solely on the perfused kidney from the day of replantation.

In group IIc the average total period of ischemia was 65 minutes, and the average relative weight gain was 22 per cent. One of these experiments is charted in Figure 7. One of the animals died 6 days after removal of the normal kidney and proved to have a thrombosis of the replant renal artery. A second dog died of cardiac arrest at the time of normal kidney resection; the replant was completely normal histologically (Fig. 8). The third dog survived removal of the normal kidney and is currently well. An excretory urogram (Fig. 9) of the replant demonstrated normal dye concentration.

DISCUSSION

It has been previously stated (2) that whole blood perfusion of excised dog kidneys at temperatures of 25 degrees C., using blood from exsanguinated animals, was subject to subnormal renal blood flow. It was not possible to sustain such flow at levels greater than 1.0 to 1.5 milliliters per gram of kidney per minute for more than 1 to 2 hours. These preparations could maintain urine production, however, for about 7 hours.

The current experiments indicated that at normal body temperature renal blood

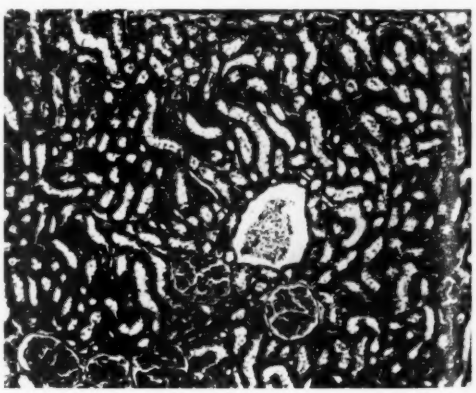

FIG. 8. Photomicrograph of kidney from group IIc, 3 weeks after autologous perfusion for 3 hours and replantation. There are no abnormalities. Hematoxylin and eosin, ×69.

flow values ranging from 3.0 to 4.0 milliliters per gram of kidney per minute could be achieved (Fig. 4 from group IIa), if the quantity of blood removed from any one donor animal was limited to 300 milliliters. The possible influence of certain humoral factors known to increase in the presence of hypotension has been discussed. These include the catechol amines and 5-hydroxytryptamine. To date, studies with numerous drugs have failed to reveal effective antagonists.

The infusion of antidiuretic hormone in amounts necessary to reduce urine flow was followed by marked reduction of renal blood flow. Verney has stated that the pump-lung-kidney preparation required 300 to 500 times the quantity of antidiuretic hormone normally effective in the intact animal.

The limited functional studies in these preparations gave results similar to those found for the hypothermic perfused kidneys, i.e., markedly subnormal creatinine clearance, creatinine filtration fraction, and creatinine urine-plasma concentration ratio. These findings presumably indicate impairment of tubular capacity for water reabsorption, perhaps in combination with glomerular injury.

Replantation of the perfused kidney. These functional abnormalities, however, were not associated with serious permanent impairment of either renal viability or capacity to support life, as borne out by the results of the perfusion-replantation experiments. Additional experiments similar to those of group IIc are necessary before the value of machine perfusion as a means of storage can be fully measured. The fact that 2 of the 3 replanted kidneys demonstrated no histologic abnormality and 1 sustained life in its recipient is encouraging. This would indicate that not only did pump-oxygenator perfusion fail to injure the organ, but also it supported extracorporeal viability for a time interval longer than the maximum duration of total ischemia ordinarily survived by these organs. Hamilton, Phillips, and Hiller and Murray, Lang, Miller, and Dammin determined that very few canine kidneys survived total ischemia greater than 3 hours' duration.

FIG. 9. Excretory urogram from dog of group IIc, demonstrating normal excretion of contrast medium by kidney which had been replanted after pump-oxygenator perfusion with autologous blood.

The experiments of group IIa, although limited in number, suggest that this technique may be applied to studies of the homograft rejection process. On histologic grounds at least, it is evident that a process which simulates classical homograft rejection can occur if the replanted kidney is perfused with mixed homologous blood. Renal transfusion reactions, which are quite uncommon in the dog, would probably not account for this microscopic pattern.

But the success of the kidney replants after perfusion by a single homologous intact animal indicates that a 3 hour exposure to homologous blood is not deleterious. Furthermore, this would indicate that the use of a whole animal, as a perfusing device, at least for this time interval holds promise as a storage device, although it lacks certain advantages of mechanical perfusion.

SUMMARY

1. The excised dog kidney in a pump-oxygenator system at normal body temperature can be perfused at virtually normal blood flow values for periods of at least 6 hours.

2. In agreement with the finding of Bayliss and Ogden, the smaller the quantity of perfusate blood withdrawn from each donor, the higher the renal blood flow achieved until the latter reaches normal levels.

3. Kidneys perfused at normothermia exhibit functional impairments similar to those perfused at 25 degrees C. The ability of such kidneys to sustain life indicates that this functional impairment is not lethal.

4. Kidneys perfused by mixed homologous blood did not survive in their original hosts; kidneys perfused by homologous blood of a single intact animal function normally and support life after replantation; kidneys perfused by autologous blood function normally and support life after replantation.

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THE EFFECT OF LOCAL FACTORS ON THE PORTAL VENOUS PATTERN

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IN THE INVESTIGATION of portal hypertension and the portal venous system, injection of x-ray contrast media into portal venous radicles has proved an invaluable clinical and experimental tool. The introduction of the transsplenic route of injection by Abeatici and Campi has been of particular value to clinicians. This technique is frequently used to determine the patency of the portal vein prior to contemplated shunt surgery. After a portacaval shunt has been performed, percutaneous splenoportography is, at the present time, the best method of determining the patency of the shunt. It has also proved extremely sensitive in the detection of esophageal collaterals. Another clinical contribution of this technique has been the demonstration of large spontaneously formed portal systemic shunts in the syndrome of episodic stupor associated with hepatic cirrhosis. Recently, Ruzicka and associates have described abnormal intrahepatic venous patterns in patients with cirrhosis of the liver.

Laboratory workers have utilized portal venography in some extremely valuable studies. Notable among these are the investigations of Daniel and Prichard, in which they were able to show by serial hepatograms effective shunting of blood through the liver under certan conditions. Child (5) and his co-workers used portal venography following portal vein ligation to study collateral formation in the monkey. In other studies, these workers (4) used this technique to follow the vascular and regeneratory changes after partial hepatectomy.

In view of the effectiveness of portography in demonstrating changes in portal venous patterns, an investigation was undertaken to evaluate the role of certain local factors, other than liver disease per se, in the roentgenologic appearance of the portal venous system.

In carrying out portal venography in the laboratory, the usual procedure has been to perform a laparotomy to inject contrast media into the portal vein or one of its tributaries. In order to obviate this, Child utilized portacaval transposition so that dye injected into the femoral vein would outline the portal venous system. Percutaneous splenoportography, unfortunately, is best carried out by using the fibrotic, enlarged spleens of patients with cirrhosis of the liver. In the dog, with a normally friable and very mobile spleen, this is an uncertain technique at best. Davis and associates have described a simple method of making the spleen available for repeated needle punctures for the purpose of intraportal injection of materials or intrasplenic pressure measurements. Briefly, it consists of transplanting a portion of the spleen into a subcutaneous pocket in the anterior abdominal wall, without disturbing its vascular attachments.

In the following report, a series of experiments on dogs is described in which serial percutaneous splenoportograms were performed in the presence of increased intra-abdominal pressure, chronic hepatic congestion, and hepatic venous outflow obstruction, either singly or in conjunction with each other.

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MATERIALS AND METHODS

This study comprises the results of 39 splenoportograms performed in 16 dogs under various conditions. Adult mongrel dogs of both sexes, weighing 10 to 20 kilograms, were used. Under intravenous nembutal anesthesia, a preliminary laparotomy was carried out, and the tail of the spleen was transplanted into a subcutaneous pocket in the anterior abdominal wall. A period of 7 to 10 days was allowed for the spleen to become firmly fixed in its new site. Percutaneous splenoportography was then performed in all animals, without anesthesia, in the right lateral decubitus position. Single exposure films at 75 kilovolts and 60 milliampere seconds were sufficient to allow detailed visualization of the extrahepatic and intrahepatic portal venous systems. Occasionally, more than one attempt at splenoportography was necessary in order to obtain complete visualization. Twenty milliliters of 70 per cent sodium acetrizoate (urokon sodium) were injected as rapidly as possible through a thin-walled, 17gauge needle. This procedure was adhered to throughout the study. Roentgenologic technique was suitably altered to obtain satisfactory roentgenograms in the presence of marked ascites. After a satisfactory control splenoportogram was obtained, 13 animals were subjected to partial constriction of the thoracic inferior vena cava, immediately above the diaphragm, to induce the formation of experimental ascites. Subsequent splenoportograms were then obtained as follows: (1) in 10 animals after 4 to 5 weeks when ascites was present; (2) 1 month after caval constriction in 1 animal in which ascites failed to develop; (3) in 2 animals 1 week after caval constriction before ascites became clinically detectable; (4) in 3 animals with ascites, splenoportograms were repeated after trocar paracentesis; (5) in 2 animals whose ascites subsided spontaneously after 6 months, splenoportography was repeated at that time. In order to assess the effect of the intra-abdominal accumulation of fluid and increased intra-abdominal pressure, without associated hepatic outflow obstruction, artificial ascites was created in 3 dogs by the infusion of isotonic saline into the peritoneal cavity through a polyethylene catheter. Splenoportograms were obtained before and after the induction of artificial ascites.

RESULTS

Repeated splenoportography by this method was generally well tolerated by the dogs. There was no mortality and no morbidity as a result of bleeding from the splenic injection site. When repeated injections were necessary for satisfactory visualization, nausea and vomiting were not infrequent.

The normal splenoportogram. The normal splenoportogram (Fig. 1) demonstrated a clearly defined, moderately tortuous splenic vein emptying into the extrahepatic portion of the portal vein. Reflux into the superior and inferior mesenteric veins was only occasionally seen. Both the extrahepatic and intrahepatic portions of the portal vein were clearly outlined, as well as the major intrahepatic portal venous branches. With the dog in the right lateral decubitus position, there was evidence of streamlining in the portal vein. Fine intrahepatic branches of the portal vein were visualized clearly in tapering fashion, extending to the periphery of the liver. These branches were discrete, evenly distributed throughout the liver, and left their parent vessel at an acute angle. In the normal splenoportogram, a faint, but distinct, blush outlined the limits of the liver. Small portal systemic collaterals were seen in the anterior abdominal wall from the area of fixation of the spleen in the subcutaneous pocket. The inferior vena cava and the azygos vein were not visualized, nor were the hepatic veins.

The splenoportogram following supradiaphragmatic inferior vena cava constriction. In the presence of ascites (Fig. 2).—The splenic vein in all cases was elongated, straightened, and narrowed. The extrahepatic portion of the portal vein was consistently narrowed

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 1. The normal splenoportogram. The entire portal venous system is clearly outlined. The fine intrahepatic branches extend to the periphery of the liver in tapering fashion. In this film, dye from a previous injection is seen in the kidneys.

FIG. 2. The splenoportogram following supradiaphragmatic inferior vena cava constriction, in the presence of ascites. The intrahepatic branches are smaller in caliber, and fewer branches are visualized. The fine branches end abruptly and do not extend to the periphery of the liver. The clip apparent in the upper portion of the film marks the location of the constricting band on the cava.

FIG. 3. The splenoportogram following supradiaphragmatic inferior vena cava constriction, before ascites became apparent. Changes in the appearance of the fine intrahepatic vessels are already present. Dye is seen in the azygos vein as portal systemic collaterals are present at this early stage. The radio-opaque lines seen above the diaphragm outline the dressing on the thoracotomy incision.

in diameter by at least 25 per cent. Definite changes were seen in the intrahepatic portal vein and its branches. Major branches appeared fewer in number and smaller in caliber in 8 cases. The number of medium-sized and fine branches visualized was also consistently decreased. In addition, the fine branches ended abruptly and did not exhibit the tapering appearance that was seen in the normal splenoportogram. Consequently, they did not extend to the periphery of the liver. These vessels were noted to leave the parent trunk at a more obtuse angle. The uniform blush that delineated the liver in the normal splenoportogram was not present. All of the dogs exhibited significant portal systemic collaterals. The most common path of collateralization was via the anterior abdominal wall, but the number and size of the vessels were considerably in excess of that which was seen to result merely from the fixation of the spleen. Intercostal, paravertebral, and retroperitoneal collaterals were visualized to a lesser extent. Dye was seen in the inferior vena cava in 5 instances. This occurred in the presence of the most extensive collateral formation. In 1 roentgenogram the azygos vein was visualized.

With failure to develop ascites.—In 1 animal, ascites did not develop following caval constriction. Subsequent splenoportography did not demonstrate any of the vascular changes which were found in those animals in whom ascites accumulated.

Before ascites became apparent (Fig. 3).—In 2 dogs, splenoportography was performed 1 week after caval constriction, before ascites became clinically detectable. It should be noted that in both of these animals ascites

subsequently developed. The splenic vein and the extrahepatic portion of the portal vein were unchanged from the control roentgenograms. The large intrahepatic portal venous branches also did not differ from the controls. However, the medium-sized and small branches were distinctly narrowed, exhibited increased angulation from the parent trunk, and did not extend to the periphery of the liver. Even at this early stage, portal systemic collateral vessels were present. In 1 of the dogs, both the inferior vena cava and the azygos vein were clearly outlined with contrast media.

Immediately following drainage of the ascites (Fig. 4).—Three animals, who underwent splenoportography in the presence of ascites, were studied again after drainage of the abdominal fluid. The splenic vein and extrahepatic portal vein resumed their normal tortuosity after the increased intra-abdominal pressure was reduced. Both the extrahepatic portal vein and large intrahepatic branches increased in caliber in 2 of the 3 animals. However, in no instance did drainage of the ascites modify the changes in the medium-sized and small vessels seen in the presence of ascites. The demonstration of collaterals was also unaffected.

After spontaneous loss of ascites (Fig. 5).—Two dogs experienced spontaneous loss of ascites approximately 6 months after caval constriction, and repeat roentgenographic studies were performed. The appearance of the splenic vein, the extrahepatic portal vein, and the large intrahepatic portal venous branches had returned to normal. In one of the animals, the medium-sized and small portal branches exhibited the pattern previously noted during the ascitic period. In the other dog, the medium-sized vessels appeared normal, but the fine vessels still demonstrated the loss of tapering and increased angulation characteristic of the ascitic pattern. Portal systemic collateral vessels were present to the same extent.

The splenoportogram with artificial ascites without inferior vena cava constriction. "Ascites" was created in 3 animals, without caval constriction, by the infusion of isotonic saline into the peritoneal cavity. Splenoportography (Fig. 6) under these conditions demonstrated in all dogs elongation and narrowing of the splenic vein and extrahepatic portal vein. The large, medium-sized, and small portal venous branches were moderately narrowed. However, there was no difference in the pattern of the fine vessels compared to the control roentgenogram. In general, the over-all hepatic size was diminished.

DISCUSSION

In this study, percutaneous splenoportography has been utilized to evaluate the significance of various factors in the production of alterations in the portal venous pattern. The normal splenoportogram, as described in the foregoing, demonstrated a characteristic appearance that has been reported previously to occur in human beings as well as in experimental animals.

The normal pattern was altered in the presence of ascites following supradiaphragmatic inferior vena cava constriction. Although there were minor degrees of variation, certain changes were always present. These were: (1) elongation and narrowing of the splenic vein and extrahepatic portal vein, (2) decrease in the caliber of the large intrahepatic portal venous branches, (3) increased angulation of the fine intrahepatic branches and loss of tapering to the periphery of the liver by these vessels, and (4) the appearance of extensive portal systemic collaterals. The experiments described have demonstrated that these changes may be divided into two categories. There are alterations that result from hepatic venous outflow obstruction and consequent hepatic congestion, and there are changes that merely reflect the accumulation of ascites and the increased intra-abdominal pressure.

It was noted that when caval constriction was not of sufficient degree to produce ascites, no change in the normal vascular pattern was effected. However, when caval constriction was sufficient to induce the formation of ascites, the vascular pattern was

FIG. 4.

FIG. 5.

FIG. 6.

FIG. 4. The splenoportogram following supradiaphragmatic inferior vena cava constriction, immediately following drainage of the ascites. Drainage of the ascites has not modified the changes in the pattern of the fine intrahepatic vessels. The demonstration of portal systemic collaterals is also unaffected.

FIG. 5. The splenoportogram following supradiaphragmatic inferior vena cava constriction, after spontaneous loss of the ascites. The loss of the normal pattern of the fine intrahepatic vessels still persists.

FIG. 6. The splenoportogram with artificial ascites without inferior vena cava constriction. There is narrowing of all the portal venous branches. The over-all hepatic size appears diminished.

modified even before detectable ascites was present. These changes were: (1) narrowing of the medium-sized intrahepatic portal branches, (2) increased angulation and loss of tapering of the finer vessels, (3) failure of these fine intrahepatic vessels to reach the periphery of the liver, and (4) the appearance of portal systemic collaterals. It is noteworthy that these were the exact findings that persisted when splenoportography was repeated after trocar paracentesis of animals with considerable ascites. The persistence of these alterations was also apparent in those dogs which experienced spontaneous remission of the ascites, without relief of the caval constriction.

Since the changes in the extrahepatic portal vein and larger intrahepatic portal venous branches were present only during the period of appreciable ascites, it is believed that they reflect the increased intra-abdominal pressure. This theory was substantiated by the roentgenograms performed when intra-abdominal pressure was increased by the production of artificial ascites, without caval constriction. The changes in intrasplenic pressure and wedged hepatic venous pressure observed during these experiments are being reported in a separate communication (3).

Bergstrand and Ekman have also made the experimental observation that increased intra-abdominal pressure alone may modify the appearance of the portal venous pattern as seen on portography. This should be borne in mind in evaluating splenoportograms in humans with cirrhosis of the liver. It is of interest that some of the findings noted in this report, particularly the alterations in the fine intrahepatic vessels and the extensive portal systemic collaterals, resemble the roentgenographic picture seen in human hepatic cirrhosis. However, the two situations cannot be exactly equated. In both instances, there is hepatic venous outflow obstruction. Although regeneratory phenomena do occur, they are not a prominent feature of supradiaphragmatic inferior

vena cava constriction. Apparently, of greater importance is the severe congestion induced by this procedure, which compresses the fine vessels to such a degree that they are no longer outlined by the contrast media. In man, on the other hand, nodular regeneration with distortion of the vessels results in a similar roentgenographic picture. In contrast to human hepatic cirrhosis, congestion and dilatation of the portal vein were not observed. This fact can be attributed to the ease and rapidity with which collateral formation occurs in the dog.

SUMMARY

1. The value of portal venography in a variety of clinical and experimental situations has been briefly reviewed.

2. A series of experiments in which serial percutaneous splenoportography was used in the unanesthetized animal to evaluate the role of various factors in the production of alterations in the portal venous pattern has been performed.

3. The normal splenoportogram has been described.

4. The changes in the normal portal venous pattern that result from hepatic venous outflow obstruction and consequent hepatic congestion have been delineated from the changes that result merely from the accumulation of ascites and increased intra-abdominal pressure.

5. The relation of these findings to the roentgenographic appearance seen in human hepatic cirrhosis has been briefly discussed.

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MORPHOLOGY OF HOMOLOGOUS AND HETEROLOGOUS TENDON GRAFTS

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PREVIOUSLY REPORTED experiments on the blood supply to normal tendons and healing grafts have shown that vascular connections between the tendon and its host are necessary for both normal gliding and functional survival (3, 4). The new blood vessels supplying free tendon grafts are intermingled with fibrous adhesions which restrict the range of motion of a new graft following the repair of human flexor tendon within the digital sheath. Thus, successful repair of human flexor tendon injuries within the digital sheath involves the elimination of the characteristics of fibrous adhesions without destroying the blood vessels which accompany them. With this goal in mind, experiments have been made with a composite tissue tendon graft which includes both flexor tendons within an intact digital sheath. It is possible to take such a graft without entering the sheath or disturbing the coiled blood vessels in the elastic mesentery which connects the sheath to the tendons. The hypothesis behind the use of this graft is that fibrous union and vascular connections could be expected to develop between the sheath and the host which would leave the gliding surface between the tendons and the sheath undisturbed. Nutrient substances and oxygen for the tendons might be transported through vessels in the mesentery which would be supplied by external connections between the donor and the sheath. Unfortunately, such a graft must be a homograft, as the highly specialized relations of tendons and sheath are found only on the volar surface of human fingers.

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An account of experiments in which composite tissue tendon grafts from human cadavers were transplanted into laboratory animals and the report of our first successful transfer of these grafts to restore flexion in human patients have already been published (5). Further experience does not indicate that these grafts should replace conventional autografts for the repair of all flexor tendon injuries within the digital sheath. However, the composite tendon homografts have been successful in extremely complex injuries in which the sheath and overlying soft tissue were also destroyed; thus, they may have definite advantages in the restoration of complicated injuries in which conventional autografts would be likely to fail.

Successful homotransplantation of composite tissue tendon grafts has raised the question of the fate of transplanted fibrocytes and their role in the persistence and function of homotransplanted tendons. Knowledge of the fate and role of fibrocytes had to be obtained before selecting a method of storage of the graft or predicting the effect of prolonged storage. In addition, the results of experiments designed to study the fate of various components of homologous tendon transplants are of some general value because all homografts, including skin, kidney, blood vessels, and endocrine organs, involve the transfer of mesenchymal tissue. In the past, epithelium has been the prime object of attention in studying the phenomenon of homologous tissue rejection. But the fate of collagen, ground substance, and mesenchymal cells may also prove to be important before all of the problems of homologous tissue transfer have been solved.

Successful restorations of animal and human tendon defects by grafting homologous

FIG. 1. Normal dog tendon. Note the relatively large number of cells.

and heterologous tendons which have been reported in past medical literature have been summarized by Peer. Review of these reports raises the question of whether the original fibroblasts and collagen persisted or whether transplanted cells were replaced by host cells which ultimately replaced the fibers as well. Transfer of tendons previously fixed in alcohol or formalin suggests that the role or condition of the transplanted fibroblasts is unimportant, but the majority of these experiments were performed upon the Achilles tendon of animals, a tendon with such a small amplitude of motion that, even after replacement by disorganized scar tissue, it functions satisfactorily. In spite of the large number of heterologous tendon transfer experiments, there is little evidence concerning the fate of cells and fibers. Replacement of cells seems more likely than replacement of fibers, because fiber replacement would require a powerful and specific collagenase, a substance which has not yet been identified in the normal tissues of human beings or laboratory animals.

This article is the report of a few experiments which were performed to answer our questions regarding the role of fibrocytes in the persistence and function of composite tendon grafts and to study the general fate of mesenchymal tissues transplanted into genetically diverse animals.

METHODS AND RESULTS

Flexor tendons from the forearms of adult mongrel dogs were transplanted into the subcutaneous tissues of the abdominal wall of mature albino rabbits. The rabbits were anesthetized with intravenous nembutal, and a midline abdominal incision was made to the depth of the anterior fascia. A subcutaneous pocket was created on both sides of the incision for a distance of approximately 2 centimeters. One of the flexor tendons from the forearm of a dog was then transplanted into the subcutaneous pocket, in a longitudinal direction. Both ends of the tendon were sutured to the underlying fascia in order to retain longitudinal orientation and a small amount of tension. In experiments in which the reactions of two different tendon preparations were being compared, the control tendon was placed in a similar subcutaneous pocket on the other side of the abdomen. The skin incision was closed with a continuous subcuticular cotton suture, and dressings were not applied. Aseptic precautions were taken during the implantation of the grafts, and the occasional rabbit which developed a wound infection or showed any abnormality of healing was discarded. Cultures were made of any suspicious transplantation sites, and only those which were sterile were included in the results of this study. Infections or abnormal inflammations produce variations in the *p*H and enzyme activity of the wound and could alter the behavior of the grafts. Repeated biopsies were not performed on a single tendon because the inflammation of a second operation might also alter the appearance of the graft.

In the first experiment, 20 dog tendons were washed with cold saline and individually wrapped in a sponge moistened with a

solution of buffered saline and antibiotics. Each tendon was placed in a separate container which was sealed and refrigerated at 37 degrees F. Two of the tendons were not refrigerated but were transplanted into rabbits immediately. Every 3 days thereafter, 2 of the refrigerated tendons were warmed in saline and transplanted beneath the abdominal wall of a different rabbit. One of the tendons was inspected 2 weeks after transfer, and the other was inspected 2 months after transplantation. Thus, dog tendons which had been stored at 37 degrees F. for periods varying between 2 days and 30 days were available for study at 2 intervals —2 weeks and 2 months—after transplantation into rabbits.

Longitudinal strength seemed approximately normal in all of the tendons at both examinations. At the 2 weeks' examination, all of the grafts showed a marked loss of transverse cohesiveness. But this striking alteration did not appear related to the length of storage of the graft. Two months after transplantation, longitudinal strength was still unchanged, and the diminished transverse cohesiveness noted at the earlier examination was not present.

Microscopically, the tendons were considerably more cellular 2 months after transfer than they were at the 2 weeks' examination. This finding was apparently caused by a dense host mononuclear cell response around the graft and an actual invasion of the collagen bundles by lymphocytes and eosinophils. It was impossible at the 2 months' examination to determine whether any of the donor fibrocytes had persisted or whether all of the cells within the tendon were host replacement cells. It did not seem that the cellular appearance of the grafts which had been stored for a long time, however, was different from the grafts transferred immediately or after only a short period of storage.

These observations suggested that heterologous tendon grafts were essentially nonliving, collagenous tissue grafts and that the condition of the cells at the time of transfer was unimportant.

FIG. 2. Degenerating fibrocytes in a dog tendon 8 days after transplantation into a rabbit.

Although these experiments strongly suggested a replacement of the donor fibroblasts by host monocytes, it was not possible to prove this theory with only 2 observations. In an attempt to follow the donor fibrocytes more closely, additional dog tendons were transplanted within the abdominal wall of rabbits. In this experiment, postoperative observations were made at 48 hour intervals. Twenty dog tendons were washed in cold saline and transplanted to rabbits immediately. Another 20 tendons were washed in cold saline and treated with 3 fresh applications of trypsin over a 24 hour period. Trypsin apparently does not affect the collagen and was used in this experiment to clear the tendons of cells and ground substance. The fresh graft was implanted on the left side of the rabbit's abdomen, and the trypsin-cleared graft was implanted on the right side of the abdomen. Thus it was possible to compare the invasion by host cells in homografts containing living donor cells and in homografts which had been cleared of donor cells and ground substance.

Every other day during the next 40 days 1 rabbit was reoperated upon, and half of

FIG. 3. Collagen bundles in a dog tendon 19 days after transplantation into a rabbit. Note the complete absence of fibrocytes and the lack of transverse cohesiveness.

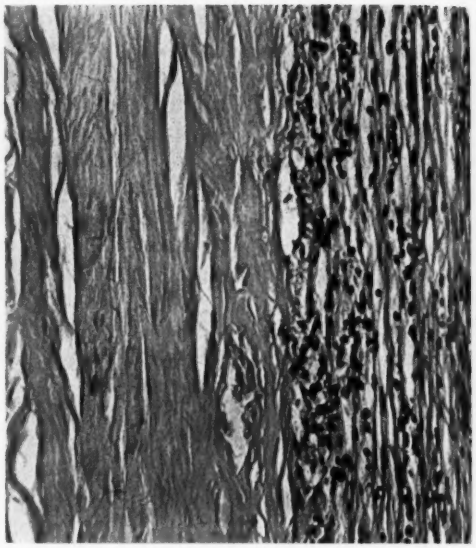

FIG. 4. Early invasion of host mononuclear cells 21 days subsequent to transplantation of a dog tendon into a rabbit.

the graft from both sides was removed for microscopic examination. Thus at the end of 40 days, there were 20 sections of trypsin-cleared tendon and 20 sections of fresh tendon grafts, a series in which each succeeding pair had remained in the host rabbit 48 hours longer than its predecessor.

Although there was considerable variation in the length of time required for cells in untreated tendons of different size and shape to react to a heterogenous host, the end results were, for the most part, uniform. In only 6 days, in exceptionally thin, flat tendons there was evidence of cell destruction. Figure 2, made from a section of untreated tendon which had been in a rabbit for 8 days, shows pyknosis and frank karyorrhexis of many of the cells. Larger, thick tendons from older dogs did not show these changes, particularly in the center of the graft, for as long as 20 days. Once the cells began to degenerate, however, the majority of them disappeared rapidly. Occasionally, it was possible to find an area where the donor fibroblasts had survived for a longer period than the cells in other areas of the tendon. This probably indicates a mechanical protection afforded some of the fibroblasts by an unusually dense accumulation of mature collagen or a relative avascularity. Particularly in old tendons, the rate of cellular death was not uniform for the whole tendon.

After death of the cells, there was a remarkably effective removal of cellular debris and a gradual disappearance of the ground substance. The collagen bundles at this time were separated by empty spaces and appeared as clean as collagen which had been artificially cleared by trypsin digestion (Fig. 3). At this stage (8 to 25 days) there was a distinct change in the gross characteristics of the graft. There was no detectable change in the longitudinal tensile strength, but the transverse strength or lateral cohesiveness between fiber bundles was markedly diminished. The fibers could be easily separated by mechanical teasing, and a silk suture could be pulled through the tendon easily. As we learned later, during the restoration of human flexor tendon injuries with a composite tendon homograft,

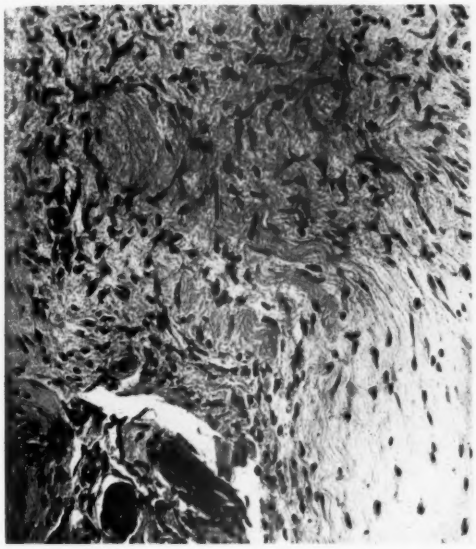

FIG. 5. Typical host cell infiltration of a dog tendon 24 days after transplantation into a rabbit. Note the random distribution and orientation of the cells.

FIG. 6. Dog tendon 36 days after transplantation into a rabbit. Note longitudinal orientation of many cells and relatively acellular appearance of center of tendon.

this is a period during which there is probably little or no new collagen formation, and healing as measured by determination of the tensile strength is virtually at a standstill. Since this period may overlap the customary 3 week postoperative immobilization period following conventional autografts, it is wise to prolong the immobilization period after homografting to 4 or 5 weeks.

During the time of cell destruction and clearing of debris, there was an accumulation of mononuclear cells around the graft which was typical of a sterile foreign body inflammatory reaction. The cells were predominantly mononuclear cells, and lymphocytes appeared to be the main cell type. The cells were packed so tightly, however, that it was difficult to identify many of them. There was a distinct absence of polymorphonuclear granular leucocytes in sterile preparations. Eosinophils were common, being most predominant during the time that cellular debris and ground substance were being removed from the graft. It is possible that the eosinophils made a preliminary contribution to the clearing process by liberating various amines such as heparin and histamine. Not until the tendon appeared completely free of donor cells and ground substance was there any evidence of an invasive movement by the surrounding host cells. About the same time when it was possible to demonstrate death and removal of the donor cells, there was a rapid invasion of the collagen bundles by surrounding host cells. In some compact thick tendons, invasion of the periphery of the tendon could occasionally be seen before the central cells had completely disappeared, but in the usual slender thin grafts there was practically no invasion of the graft until the donor cells had completely disappeared. Figure 4 is a photomicrograph of a dog tendon heterograft which had been transplanted beneath the anterior abdominal wall of a rabbit for 21 days. Fortunately, the sequence of events was stopped at a time when cellular clearing had been superbly accomplished and host invasion was just beginning. Such a section is difficult to obtain because the formation of the host capsule and the re-

FIG. 7. Dog tendon following digestion of cells and ground substance by trypsin.

FIG. 8. Early invasion of host mononuclear cells 3 days after transplantation of dog tendon into a rabbit.

placement of donor cells by an invasion of cells from this capsule is an inflammatory reaction which proceeds with a velocity typical of other inflammatory reactions. The host cells in the capsule surrounding the tendon almost seem to be poised at the periphery awaiting the opportunity to invade the graft the instant that all of the donor cells have been removed. A large number of slides from tendons at various stages of host acceptance were examined before one was caught at the exact moment seen in Figure 4. However, this slide demonstrates the typical mechanism and sequence of events that occur during host acceptance of a homologous or heterologous tendon graft. The exact time sequence and completeness of the reaction may vary with tendons of different size, shape, and age, but acceptance of the graft, as far as can be told from these experiments, involves the steps which are depicted in this slide.

Invasion of the graft continues at a rapid rate until the entire transplant has been overrun with host cells. Four to 6 weeks after transplantation, the tendon homografts are 3 or 4 times as cellular as normal tendons. It was difficult to identify all of the cell types in our preparations, but since lymphocytes have the embryonic potential to metamorphose into histiocytes and fibroblasts, it seems probable that the inflammatory response to a foreign body attracts into the area lymphocytes which eventually become mature fibroblasts. The cells appear randomly distributed at first (Figs. 5 and 6) but later become partially polarized in a longitudinal direction. It is possible that polarization is more pronounced in a functioning digital tendon graft than in a relatively adynamic subcutaneous implant beneath the abdominal wall. Furthermore, polarization probably occurs according to the stress placed on the collagen and may even reflect a demand for new collagen to be formed in a predetermined direction. Almost simultaneously with the invasion of host cells, it is possible to demonstrate an appreciable return of transverse cohesiveness and lateral stability. The combination of new cells and ground substance is undoubtedly responsible for new collagen production because the strength of union between autogenous and heterogenous tendons

rapidly assumes normal proportions. Thus, healing between the tendon ends is apparently dependent upon acceptance of the new graft by the host organism.

Tendons which had been treated with trypsin prior to implantation progressed through the same process of host cell invasion as the fresh grafts except that they did not have to wait for death and removal of the donor cells before invasion by host cells began. Host cells can be seen invading the graft shown in Figure 8 three days after implantation; from this point on, the acceptance of the graft follows the same steps as described for fresh untreated grafts. Although cellular invasion of trypsin-digested grafts occurred earlier than in untreated grafts, the time interval necessary for complete invasion varied over an even wider range. This was probably because the different size and age of various tendons hampered the efficiency of the digestive process. Even following pretreatment with hyaluronidase, trypsin digestion was sometimes incomplete except in very thin, flat tendons from young animals. The collagen is so compact in the center of some tendons that trypsin does not reach the cells; therefore, many of the grafts contained areas which were completely clear of cells and debris as well as other areas which contained normal appearing fibrocytes. On the whole, however, we gained the definite impression that grafts in which all of the cells were digested by trypsin were invaded by host cells in from 5 to 15 days earlier than fresh untreated grafts.

DISCUSSION

The results of these experiments show that homologous and heterologous tendon grafts are primarily collagen transplants. To use Longmire's classification, they are purely homostatic grafts which are incorporated into the host only after all of the transferred cells have been destroyed and replaced by host cells. The variable length of time required to accomplish donor cell destruction and host cell replacement is probably related to the variable physical properties of dog tendons. Presuming that the death of the fibrocytes is due to a cytotoxic antibody which is a macromolecular antibody similar to or identical with epithelial antibodies, it is conceivable that the collagen bundles could function, at least temporarily, in the same manner as an artificial millepore filter. Anyone having experience in cutting sections of dog tendons will attest to the wide variation in compactness and toughness of these structures. Some dog tendons have a consistency approaching bone, and often wreck the microtome knife as they are sectioned, while other tendons from younger animals are quite easy to section. The solubility, thermal contractions, and swelling properties of collagen fibers are all affected by the more extensive polymerization that occurs with the aging of collagen, and these variable physical and chemical characteristics might conceivably alter the protection which the collagen bundles afford deeply imbedded fibrocytes. All that was observed in these simple experiments is a variation in the life span of transplanted cells which does seem to correlate with the size and age of the tendon. If we are correct in the hypothesis that the physical compactness of certain areas of the tendon affords more or less mechanical shielding from cellular antibodies, it is conceivable that tendon homografts could exist with the donor cells intact for even longer periods than were observed in our experiments.

Although there is no proof of the exact mechanism of death of the transplanted fibroblasts, it seems probable that they carry tissue specificity antigens which excite an antibody response in the host. The "second set" rejection phenomenon which is the strongest evidence available for the immunologic basis of foreign tissue rejection is extremely difficult to demonstrate with fibroblasts because of the wide variation in survival time of these cells in different tendons from the same animal. It is currently believed, however, that all nucleated cells carry specificity antigens. There is no reason

to suspect that fibroblasts are deficient in antigenic specificity. Their death is presumed to be due to cytotoxic antibodies. Yet, if this were certain, our experiments would raise strong objections to the popular hypothesis reported by Lawrence that homologous tissue rejection is an immunologic reaction of the delayed hypersensitivity type. Delayed sensitivity reactions are believed to involve macromolecular antigens and antibodies which are attached to cells and are not circulating freely in the serum or extracellular tissue juices. Passive transfer of cellular immunity has not been possible by the transfer of serum or dead tissue, although Stetson has recently suggested that the possibilities of such a transfer have not been completely explored.

We have never recognized a single host cell in the interior of a tendon homograft until after the donor cells have been destroyed and removed. It seems highly unlikely that lymphocytes or other reticuloendothelial cells could circulate in these grafts and not be recognized in any of the many sections that were examined. From our observations, it is concluded either that the donor fibroblasts do not carry specificity antigens and are therefore not the victims of an antibody attack, or that tissue antibodies are not always attached to reticuloendothelial cells. These are fundamental questions concerning the mechanism of tissue rejection which are obviously beyond the scope of the experiments reported in this article. Our experiments do point out, however, that the study of simple, relatively acellular tissues, such as tendon or cartilage, can afford an opportunity to explore and evaluate some of the fundamental concepts relating to the general mechanism of tissue rejection.

SUMMARY

In anticipation of a trial of composite tendon homografts of the flexor mechanism, heterologous tendon transplants were observed after varying periods of refrigerated storage. The persistence of the graft and eventual invasion by mononuclear host cells were not affected by storage at 37 degrees F. for periods up to 40 days before transplantation. The fate of the transplanted fibrocytes was determined by examining fresh and artificially altered heterologous tendon grafts at 48 hour intervals for 45 days. Eventually, all of the donor fibrocytes were removed and a complete invasion of the graft by host mononuclear cells occurred. Host acceptance of the graft and eventual healing between tendon ends were apparently coincident with replacement of the donor cells by host fibrocytes. The mechanism of cellular replacement and its possible significance in the general problem of homotransplant rejection were discussed.

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CONTINUOUS BLOOD *p*H MEASUREMENT WITH EXTRACORPOREAL COOLING

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THIS REPORT is written to show in detail a method of continuous blood *p*H measurement. In 35 animal experiments in which the body temperature has been reduced from 37 to 25 degrees C. in less than ½ hour with rewarming effected in the same period of time, it has been necessary to hold the blood *p*H within rather narrow limits. To measure the blood *p*H properly, a continuously indicating blood *p*H meter is required. By controlling the blood *p*H, there has been no animal loss from ventricular fibrillation or rewarming shock which are 2 of the 3 major complications of hypothermia described by Bigelow. Since control of the blood *p*H directly affects these 2 major complications associated with hypothermia, the method used to continuously measure the blood *p*H seemed worthy to report in some detail and is the basis for this article. Details of the cooling technique and results of the experimentation will be reported upon in subsequent articles.

As we learn more about the physiology of hypothermia it becomes evident that the alterations which occur on the hydrogen ion concentration of the blood at reduced temperatures have direct bearing on the function of the cardiovascular system. That this effect on the function of the heart by the hydrogen ion is an indirect one and probably due to its effect on the cell membrane which in turn produces gradual alterations in the concentration of the major electrolytes of the blood, such as potassium, sodium, and bicarbonate, has been pointed out by Roberts and Magida. Burnell and his associates have elaborated on and quantitated the inverse relationship between blood *p*H and serum potassium levels. Harkins, using intravenous hydrochloric acid, demonstrated in animals that it was possible to depress the blood *p*H acutely to 6.12, a level previously considered incompatible with life. This reaction in itself did not cause death, in most cases, but produced profound alterations in the acid-base equilibrium and caused water and chloride to move into the cell. Ross has observed that acidotic dogs have an increase in the hematocrit of 10 per cent during cooling but alkalotic dogs have a decrease of 3 to 6 per cent at 25 degrees C. The blood *p*H level can thus indirectly control the blood volume and the major blood and cellular electrolyte constituents.

As mentioned the 3 main problems associated with hypothermia are rewarming shock, ventricular irritability (ventricular fibrillation), and increased bleeding time. Rewarming shock was first described by Blair, Montgomery, and Swan. At that time the cause was not known, but later Fawley, Waddell, and Bigelow observed that the fall in blood pressure with rewarming was associated with a decrease in the blood *p*H which if corrected in time would prevent death from shock. In the present series, a decrease in the blood *p*H has repeatedly been observed with rapid warming, and it has been necessary to elevate the blood *p*H artificially with electrolytes to prevent the so-called rewarming shock. Further evidence of the effect which the blood *p*H level has on the function of the heart is illustrated by the inability to defibrillate the dog heart at 25 degrees C. if the blood *p*H is over 7.30.

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DESCRIPTION OF BLOOD *p*H TRANSDUCER

General. A *p*H meter is an electrochemical transducer used to measure the hydrogen ion concentration or *p*H. Two electrodes are immersed in the liquid under test. One electrode has a constant potential with respect to hydrogen regardless of the *p*H of the liquid. A saturated solution of calomel (mercurous chloride) is most often used. The other electrode must have a potential output with respect to hydrogen which varies with *p*H, and is often a so-called glass electrode.

Figure 1 is a photograph of the blood *p*H transducer showing its various parts. The unit plugs into the corporeal cooling circuit at the desired position by use of the 2 stainless steel adapters designed for ¼ inch internal diameter tubing used in the circuit. The *p*H value with this technique is unaffected by changing flow rates from 0 to 2,500 cubic centimeters per minute, the maximum pumping capacity of the system. Once standardization has been accomplished with a solution of known *p*H, continuous readings of the blood *p*H are available on a calibrated meter for a period of many hours with no further attention to the instrument required. The only requirement of the blood is that it be heparinized sufficiently to prevent clotting on the glass electrode. The entire unit can be taken apart for cleansing and sterilization.

Construction. The *p*H transducer is constructed from the following 5 component parts as seen in Figure 1:

1, The square acrylic plastic cuvette has a volume of 10 cubic centimeters and is designed so that clotting does not occur either on the surface of the inserted glass electrode or on the walls of the cuvette chamber. Clotting in the chamber is prevented by the use of acrylic plastic with a high surface polish and circular configuration of the chamber to reduce turbulence of the blood. Clotting over the surface of the inserted glass electrode is prevented by directing the inflowing blood against the soft glass sensing head of the electrode. A symmetric laminar flow of blood around the tip of the electrode prevents fibrin formation.

2, The tapered glass electrode inserts into the cuvette and is held by friction alone. During cleansing of the corporeal cooling system it is replaced by a stainless steel plug since harsh alkalies and soap are damaging to the glass electrode. When not in use the glass electrode is kept in normal saline solution. All glass electrodes become inaccurate if allowed to dry because of the hygroscopic characteristic of soft glass used as the sensing element in glass electrodes.

3, The calomel electrode is a conventional commercial cell. Its absolute value in terms of reference voltage is unimportant as long as the value does not change during the time of the *p*H measurements. This is assured if the room temperature is kept constant and if the potassium chloride solution in the electrode has had sufficient time to come to thermal equilibrium with the room air. Since the pressure of the circulating blood is increased in relation to the atmospheric pressure, means must be taken to equalize the pressure at the surface of the potassium chloride solution in the calomel cell with the blood, or a gradual back flow would occur into the calomel cell destroying its standard voltage reference level and throwing the *p*H values off. In this method, back flow is prevented by the use of a 3-way stopcock and a short piece of rubber tubing to keep the pressure at the liquid surface of the calomel cell equal to that at the calomel salt bridge junction. This same 3-way stopcock allows the salt bridge into which the calomel cell inserts to be bled free of air at the start of the measurements.

4, The function of the rather long normal saline salt bridge is twofold. It prevents clotting of the blood at the calomel electrode junction which would occur because of the concentrated potassium chloride solution coming into contact with the blood, and it also provides thermal isolation of the calomel cell by keeping it distant from the warm or cool blood and thus constant from the reference voltage aspect. The physical components of the salt bridge starting at the cuvette are a 6 inch length of intravenous tubing

with a needle hub adapter to insert into the 2-way stopcock at the cuvette. Into the opposite end of the tubing is inserted the narrow end of a calcium chloride drying tube which in operation is held by a ring clamp. A suitable 2-holed rubber stopper with the calomel cell inserted into one hole and the previously mentioned 3-way valve inserted into the other hole is inserted into the cut-off end of the calcium chloride drying tube and adjusted so the tip of the calomel cell is well below the level of the heparinized normal saline which fills the bridge. An additional unanticipated advantage of this salt bridge is that the long length of the connecting salt bridge tubing keeps the blood-normal saline solution interface in the tubing. As a result, very little mixing of the blood and normal saline solution occurs. As mentioned, any clot that might occur either in the tubing or over the tip of the calomel cell will destroy the reliability of the system.

5, The stainless steel grounding plate is a most important and often overlooked part of any remote measuring *p*H system. Without it, touching the apparatus or movement of the tubing causes wild variations in the *p*H meter indications. This grounding plate serves as the covering of the cuvette and is held in position by 4 bolts and wing nuts against an O ring seal on the cuvette providing a blood-tight seal. A small button is silver-soldered onto the plate to which the blood grounding clip is attached. Proper blood grounding also allows operation in areas of high 60 cycle interference from the power mains.

*The p*H *amplifier*. A commercial and not a laboratory model is used. The commercial version is designed to operate continuously over periods of many months. However, the choice of this meter was affected by several other considerations. The meter is panel-mounted in a hermetically sealed case which lends itself well to use in our control panel along with the other instruments. Most important is the isolated blood ground and the differential input provided. The use of the differential input allows accurate *p*H readings to be taken in locations where single-ended measurements (common to most laboratory instruments) would be impossible because of electrical interference. Figure 2 is a diagram of the circuit used.

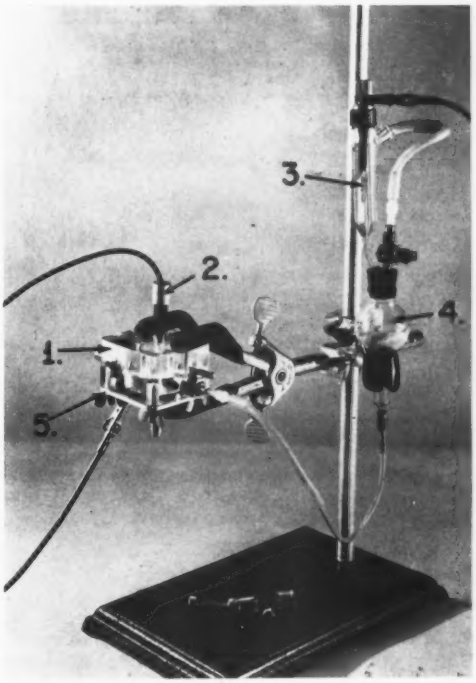

FIG. 1. Blood *p*H transducer: *1*, square acrylic cuvette, *2*, tapered glass electrode, *3*, calomel reference cell, *4*, salt bridge, *5*, stainless steel grounding plate.

OPERATION OF BLOOD *p*H METER

Standardization of the system is accomplished after the meter has been turned on for ½ hour which allows the amplifier to stabilize and prevents drift. The glass electrode and calomel electrode have been placed in a 1 to 1,000 zephiran solution for 24 hours. Sterility of the *p*H 7 standard buffer solution is obtained by autoclaving in a stainless steel container the night before. Standard solution is kept in polyvinyl containers when stored. The volume of the *p*H 7 standard solution is noted at the start of autoclaving; when finished any volume difference is replaced with sterile distilled water.

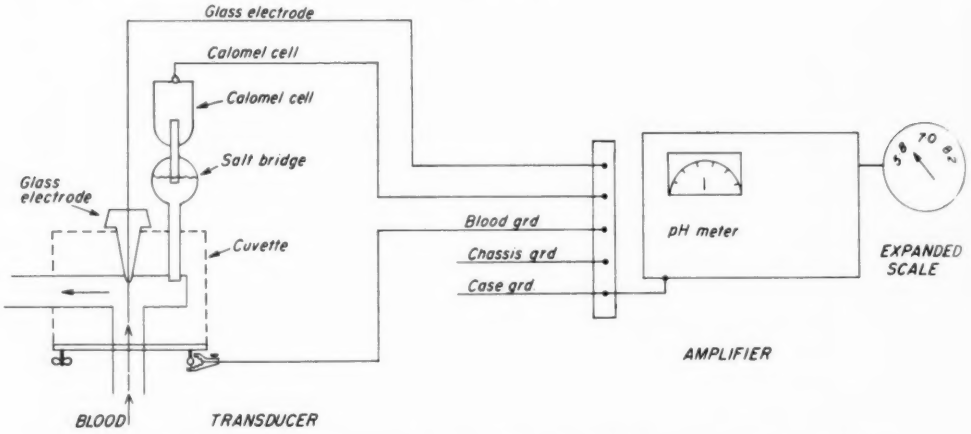

FIG. 2. Circuit diagram of continuous flow blood *p*H monitoring system. The blood *p*H transducer is kept near the extracorporeal cooling system, while the amplifier and expanded scale are built into the control panel near the anesthesiologist who makes the necessary *p*H corrections. The expanded scale permits easy reading of the blood *p*H to ±0.02 *p*H units.

The salt bridge assembly is autoclaved. It is then filled with normal saline solution to which 15 milligrams of heparin per 500 cubic centimeters of saline solution have been added. The sterile calomel cell and rubber cork are inserted into the salt bridge assembly, and the 3-way stopcock is turned so that pressure equalization occurs between the surface of the calomel cell and the surface of the salt bridge. The tip of the calomel cell should extend well below the surface of the normal saline solution in the bridge. The glass electrode and the cuvette end of the salt bridge are inserted into the cuvette containing the *p*H 7 standard solution. The meter is standardized to the calomel cell and glass electrode. The meter is locked in stand-by position. The cuvette is flushed of *p*H 7 solution and then filled with normal saline solution. After blood is flowing through the cuvette, the meter is switched so that readings can be obtained. Continuous blood *p*H indication is then available on an expanded scale (*p*H 5.8 to 8.2) without further attention to the meter. The salt bridge may be flushed with normal saline if clots are suspected and then reinserted into the cuvette without stopping blood flow through the cuvette or affecting calibration.

RELATIONSHIP OF *p*H TO TEMPERATURE

A few words about the relationship between blood *p*H and blood temperature are appropriate at this time. A common misconception is that human, dog, or ox blood in vivo becomes more alkaline as the temperature of the blood is reduced. This is a fallacy as shown by Brewin. If blood is drawn anaerobically at 37 degrees C. and cooled in the same container and read at 27 degrees C., the indicated blood *p*H actually will be more alkaline than at 37 degrees C. This shift in the blood *p*H with temperature has been described by Rosenthal and Craig. Rosenthal gave the relationship

$$pH_{38} = pH_t - .0147\ (38 - t)^1$$

where (t) is temperature of measurement. Hence blood stored anaerobically with *p*H at 38 degrees C. equals 7.4 would have a *p*H at 18 degrees C. of 7.69.

The reason blood becomes more alkaline when drawn anaerobically at one temperature and read at a lower temperature is that it re-equilibrates. But with respect to the problem of hypothermia, this fact is irrelevant. The condition described cannot occur

[1]Both Rosenthal and Craig use 38 degrees C. as normal body temperature while we use 37 degrees C. This fact does not affect the slope of the curve.

in the cooled animal. In the words of Brewin and associates: "The carbon dioxide combining power of such blood increases as the protein ionization decreases owing to the fall of temperature and the extra CO_2 consequently combined as bicarbonate is derived from dissolved CO_2 and therefore the pCO_2 falls. Hence the plasma becomes more alkaline. The circumstances in experimental hypothermia are entirely different and the resulting changes must be determined directly." From a clinical aspect the important thing to remember is that blood at 37 degrees C. will have the *same* *p*H at 27 degrees C. or 17 degrees C. if the carbon dioxide pressure is held the same and a metabolic acidosis or alkalosis has not developed. The advantage of continuous *p*H measurement during the course of hypothermia becomes obvious.

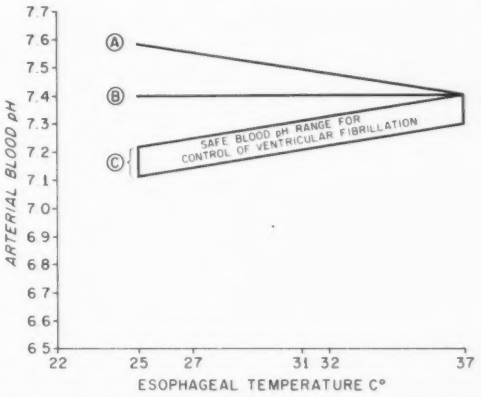

FIG. 3. Graphic illustration of relationship between blood *p*H and blood temperature. *A*, Volume per cent carbon dioxide in blood held constant: $pH_{38}=pH_t-.0147\ (38-t)$. *B*, Partial pressure of carbon dioxide in blood held constant: $pH_{37}=pH_t$. *C*, pH_t or thermic optimum level for blood *p*H during hypothermia: $pH_t=7.35-.015\ (37-t) \pm .05$.

OPTIMUM *p*H AT REDUCED TEMPERATURE

Although optimum values of blood *p*H at different temperatures are yet to be determined, experimentally it was found that at reduced body temperatures lowered blood *p*H levels reduce cardiac irritability and the incidence of ventricular fibrillation and make defibrillation possible. If, at normal temperature, optimum blood *p*H is 7.35 then the desired blood *p*H level (plus or minus .05 *p*H) with temperatures is approximated by

$$pH_t=7.35-.015\ (37-t)$$

where (t) is temperature in degrees centigrade and pH_t is the optimum *p*H at that body temperature. From this, pH_t at 27 degrees C. would be 7.20. In practice we try to hold the blood *p*H below 7.3 with body temperature below 31 degrees C. while cooling because otherwise ventricular fibrillation frequently develops. At body temperature of 25 degrees C. it has not been possible to defibrillate the heart if the blood *p*H is over 7.2. In 1 instance with a body temperature of 24.8 degrees C. spontaneous ventricular fibrillation occurred when the blood *p*H was 7.3. Repeated attempts at defibrillation with intervening periods of cardiac massage over a 22 minute period of time were unsuccessful. On lowering the blood *p*H to 7.1 using acid electrolytes (308 mEq. HCl) defibrillation occurred on the first attempt. Rewarming was uneventful.

Figure 3 is a graphic illustration of this concept of the relationship between blood *p*H and blood temperature. In curve *A* is seen a gradual rise in blood *p*H with cooling if the *amount* (volumes per cent) of carbon dioxide in the blood is held constant. The blood *p*H increases .147 *p*H units with each 10 degrees C. of fall in blood temperature. This statement is based on Rosenthal's demonstrated in vitro relationship. When the partial pressure of carbon dioxide is held constant with cooling as in curve *B* of Figure 3, the blood *p*H remains constant with cooling. The amount of carbon dioxide in the blood would have to be increased to affect this condition. Curve *C* of Figure 3 approximates what has been experimentally derived as the safe area of arterial blood *p*H with cooling if myocardial irritability is to be prevented and ventricular fibrillation controlled at reduced temperature. It is the area of plus or minus 0.05 *p*H along the curve

$$pH_t=7.35-.015\ (37-t)$$

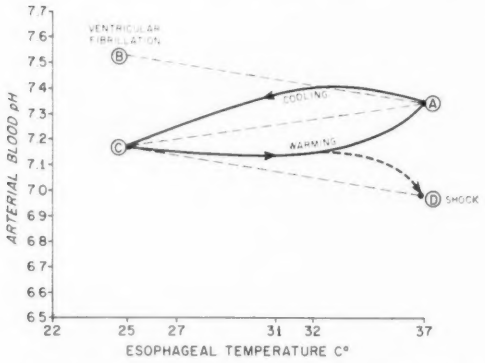

FIG. 4. Blood *p*H curve obtained with corporeal cooling and warming while controlling the blood *p*H with electrolytes.

where pH_t is the optimum blood *p*H at blood temperature (t) in degrees centigrade. Attesting to the validity of this approximation is our ability to control ventricular fibrillation easily at 25 degrees C. by electric defibrillation, if the blood *p*H is below 7.20. This observation applies to 35 dogs in which the body temperature was reduced to 25 degrees C. in less than ½ hour in the attempt to stay within the defined area of blood *p*H. Depressing the blood *p*H at lowered temperatures is not without its own hazard. It prevents or enables control of ventricular fibrillation, but if levels below *p*H 6.8 at body temperature of 25 degrees C. are reached the blood pressure drops and a shock-like condition develops. Control of the blood *p*H level is affected by use of hydrochloric acid or sodium hydroxide at concentrations of 308 milliequivalents per liter while hyperventilating the animal.

Figure 4 illustrates the average type of curve obtained with rapidly cooling and warming the animal by extracorporeal heat transfer. The esophageal temperature of the dog is cooled from 37 to 25 degrees C. in 20 minutes by circulating blood from the left femoral artery to heat exchanger to left femoral vein at 20 cubic centimeter per kilogram of body weight per minute. Warming is also done in 20 minutes. At (*A*) the beginning of cooling the arterial blood *p*H is 7.35. If the amount of carbon dioxide in the blood is held constant with cooling by controlling the respiration the blood *p*H increases to 7.53 at 25 degrees C. (*B*). It has not been possible to stop ventricular fibrillation at this esophageal temperature and blood *p*H. By the slow addition of a solution containing 308 milliequivalents per liter of chloride as hydrochloric acid during cooling, the blood *p*H is reduced to 7.17 at 25 degrees C. (*C*). At this temperature and blood *p*H, spontaneous or artificially induced ventricular fibrillation is easily controlled by electric defibrillation. Now with warming, without the addition of an alkaline electrolyte, the blood *p*H will gradually fall to 6.99 or below at 37 degrees C. (*D*) producing shock. However, by the slow addition to the extracorporeal circuit of alkaline electrolyte as a solution containing 308 milliequivalents per liter of sodium as sodium hydroxide, a gradual rise in blood *p*H occurs with temperature. Giving an amount of sodium hydroxide solution during warming equivalent to the amount of hydrochloric acid solution given during cooling returns the blood *p*H to 7.35 at the end of rewarming (*A*). Equivalent amounts of the acid and alkaline solutions when mixed result in a normal saline solution. Average total amounts required are 3 to 4 milliequivalents per kilogram of body weight each of chloride and sodium. This represents a volume of normal saline solution addition of 20 to 27 cubic centimeters per kilogram of body weight at the completion of cooling and rewarming. Such an amount given over the time required for the heating and cooling does not produce a serious hemodilution since the kidneys at reduced temperature continue to excrete water and saline at an increased rate.

In several instances, an attempt has been made to produce rapid corporeal cooling and warming by giving an arbitrary amount of 3 milliequivalents per kilogram of body weight of chloride as hydrochloric acid during the cooling, and then during the rewarming by giving 3 milliequivalents per

kilogram of body weight of sodium as sodium hydroxide. This attempt has been unsuccessful because the blood *p*H is not always the same at the start of cooling, the amount of spontaneous metabolic acidosis which develops cannot be calculated in advance, and the amount of chloride excreted by the kidneys is not constant. To control the blood *p*H by using electrolytes it is necessary to use a continuously indicating blood *p*H meter and to adjust the blood *p*H as indicated by the meter.

DISCUSSION

When hypothermia is rapidly induced by a corporeal cooling system and adequate oxygenation is maintained by a respirator, the blood *p*H increases. Also, myocardial irritability increases at reduced temperature. An increased blood *p*H further accentuates the myocardial irritability, and if ventricular fibrillation develops it may be impossible to control. By decreasing the blood *p*H at lowered body temperature, myocardial irritability is reduced, and if ventricular fibrillation develops it is controllable by a conventional electric defibrillator. Adequate oxygenation is assured, and elevated blood *p*H commonly associated with artificial ventilation and hypothermia is prevented.

With rapid warming by a corporeal heating system, rewarming shock tends to develop in the later phase of the heating. This is associated with a decreasing blood *p*H that is probably the cause of the shock. The shock is prevented by elevating the blood *p*H.

The use of electrolytes to control the blood *p*H permits independent control of oxygenation and blood *p*H. By monitoring and making necessary corrections in the blood *p*H, ventricular fibrillation and rewarming shock can be controlled. This control makes a safer procedure of hypothermia by preventing 2 of its 3 major associated complications.

CONCLUSIONS

1. A technique of continuous blood *p*H measurement is described.

2. On the premise that ventricular fibrillation and rewarming shock are 2 of the 3 major hazards associated with hypothermia, it has been found that by controlling the blood *p*H during rapid corporeal cooling and warming by use of acid or alkaline electrolytes, it is possible to control the former at reduced temperature and prevent the latter from developing at the end of warming.

3. The relationship between blood *p*H and temperature shift is discussed.

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SELECTIVE HYPOTHERMIA OF THE HEART IN ANOXIC CARDIAC ARREST

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ANOXIC CARDIAC ARREST is taking its place among methods of elective cardioplegia. Despite Wesolowski's early observations that cardiac activity could be re-established after prolonged anoxia, resuscitation is uncertain after more than 20 minutes of continuous myocardial anoxia at normal temperature. Cross and his associates have extended the period of safe anoxia by perfusing the coronary arteries with cold blood after induction of potassium arrest. This work introduced the concept of selective cardiac hypothermia.

Gollan, Sealy, and their associates incorporated heat exchangers into their extracorporeal circulatory systems to accomplish general hypothermia in combination with the heart-lung machine. Selective hypothermia has appeal because of the rapidity with which the myocardial temperature can be restored to normal. Refinements in artificial heart-lung apparatus have rendered obsolete the low flows permitted with adjunctive general hypothermia. Moreover, indictment of potassium arrest is now substantiated well enough to justify a systematic search for methods to enhance the safety and duration of anoxic arrest. Again, selective hypothermia of the heart emerges as a logical route to prolonged, reversible myocardial anoxia.

This investigation was designed to study selective hypothermia of the heart induced by simple perfusion of the suspended pericardial sac with cold isotonic saline. Suture fixation of a small catheter at several points along the rim of the pericardial cradle provided a satisfactory method for irrigating the heart. Saline at 0 to 5 degrees C. accomplished the heat transfer when administered at a rate of about 30 milliliters per minute through the multiholed catheter. The solution in no way obscured the operative field and in fact contributed to identification of structures by washing away whatever blood was present.

Periods of cardiac anoxia as long as 1 hour were well tolerated in dogs during selective hypothermia of the heart while the remainder of the body was perfused with blood at normal temperature.

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METHOD

Adult mongrel dogs of either sex were anesthetized with intravenous pentobarbital sodium and submitted to right thoracotomy through the fourth intercostal space. The caval cannulations were carried out after approximately 1.75 milligrams per kilogram of body weight of heparin were given into the right atrium. The pericardium was sutured to the muscular edges of the incision to exclude lung tissue from the operative field and to provide a reservoir for the cold saline solution. A No. 10 F. catheter was placed in the left atrium through a convenient pulmonary vein so that bronchial return was deflected into the oxygenator. Some bronchial drainage gains access to the pulmonary artery, but in the absence of a septal defect the pulmonary artery does not effectively decompress the left atrium. The ascending aorta was dissected to permit its occlusion independent of the pulmonary artery. The femoral artery was used to direct blood from the

TABLE I.—PRELIMINARY GROUP (NO CARDIAC HYPOTHERMIA)

No.	Weight, kgm.	Flow rate, ml./min.	Duration of cardiac anoxia, mins.	Duration of machine support, mins.	Total bypass time, mins.	Ventricular fibrillation	Fate
1	18.6	1200	8	22	35	None	Long term survivor
2	14.1	1500	10	25	40	With release of aortic occlusion	Long term survivor
3	13.7	1200	15	20	38	After 6.5 mins. aortic occlusion	Long term survivor
4	18	1800	15	25	42	Induced	Long term survivor
5	16	1500	15	25	45	Induced	Long term survivor
6	16.3	1400	15	17	35	Induced	Long term survivor
7	18.2	1400	15	55	72	Induced	Long term survivor
8	19	1400	20	30	55	Induced	Long term survivor

TABLE II.—THIRTY MINUTES OF CARDIAC ANOXIA WITH HYPOTHERMIA OF THE HEART

No.	Weight, kgm.	Flow rate, ml./min.	Duration of machine support, mins.	Total bypass time, mins.	Ventricular fibrillation	Fate	Temperature C. ° R.V.	L.V.	Body
1	22	1400	30	62	Induced	Long term survivor	—	—	—
2	19	1400	25	60	Induced	Long term survivor	—	—	—
3	17.3	1400	20	55	Induced	Long term survivor	—	—	—
4	13.7	1000	22	55	Induced	Long term survivor	—	—	—
5	13.6	1400	15	50	Induced	Long term survivor	24	28	34

oxygenator into the systemic arterial circulation. A rotating disc oxygenator was utilized in all experiments. The contralateral femoral artery was cannulated for continuous registration of pressure.

A 4 to 6 centimeter right ventriculotomy was performed in each animal so that recovery from the period of anoxia would be comparable to the clinical situation. Functional inefficiencies of right ventricle after ventriculotomy were noted by Stirling.

Since ventricular fibrillation was inevitable because of the cardiotomy in an anoxic heart further stimulated by local cold, fibrillation was induced in some experiments immediately after occlusion of the aorta. A weak shock of 20 to 30 milliamperes in strength and 0.1 second in duration was delivered to the heart surface by means of bipolar electrodes. An S-4-D Grass stimulator generated the stimulus. Duration of the stimulus was intentionally long to project into the vulnerable period. No signal synchronization circuit was utilized. Defibrillation was routinely and uniformly effected by a countershock of approximately 1.5 amperes and 0.01 second. No effort was made to defibrillate until coronary circulation was established for at least 5 minutes after disocclusion of the aorta. Simultaneously with removal of the aortic clamp both caval chokers were released to prevent heart dilatation on the right side. The left atrial catheter was not withdrawn until defibrillation was accomplished. In some animals in which the vigor of fibrillation did not increase rapidly with restitution of coronary flow, 0.1 milliliter of 1:1,000 epinephrine was injected into the left ventricle before massage and electric shock restored regular rhythm to the heart. The need for epinephrine did not correlate with the duration of anoxia or the degree of myocardial hypothermia.

The ventriculotomy was made before cross-clamping the aorta and repaired a few minutes before its release. The heart assumed full responsibility for the circulation by increments while pump-oxygenator support was gradually diminished.

The experimental design was established

after a preliminary series of dogs was submitted to from 8 to 20 minutes of cardiac anoxia during bypass with the heart-lung machine, but selective cooling of the heart was not used. After this pilot group, 3 series of dogs were subjected to 30, 45, and 60 minutes respectively of cardiac anoxia; selective cardiac hypothermia was induced in all by irrigating the myocardial surface with normal saline at from 0 to 5 degrees C. Myocardial temperatures were recorded at intervals in some animals by means of a thermistor on the tip of a 22 gauge hypodermic needle. Body temperature was maintained by the heating element on the oxygenator. Three infrared bulbs under the oxygenator provided an efficient heat source.

Arterial pressure seldom dropped below 80 millimeters of mercury except for the few moments after release of aortic occlusion when the diminution in resistance was reflected immediately by a transient fall in blood pressure. Flow rates were held in the area of 60 to 100 milliliters per kilogram per minute. No change in arterial flow was made during the course of the perfusion except when the animal was weaned from his extracorporeal source of support. Blood from the cavae and left atrium was returned to a reservoir by gravity and pumped from the reservoir into the oxygenator.

The liter or 2 of cold saline was aspirated and discarded. The amount of blood also discarded was minimal even when occlusion was maintained for 1 hour. Bronchial flow reaching the right ventricle from the pulmonary artery constituted the only source of blood in the operating field. Most of the bronchial return was picked up by the left atrial catheter.

In the preliminary group, no left atrial catheter was used, and in 1 of the hour-long occlusive experiments the left atrial catheter was purposely omitted. This resulted in the only death in any group. The left side of the heart and pulmonary venous system were distended, and the additional mass detracted from the efficiency of the cooling.

No untoward effect could be attributed to the use of a long-acting barbiturate in patient animals. Blood for priming the oxygenator was drawn by gravity from the carotid arteries of dogs anesthetized with pentothal sodium. Twenty milligrams of heparin per 500 milliliters of blood sufficed to prevent clotting. Siliconed glass containers, 2,000 milliliters each, were used to collect blood from donor animals. Each experiment required 3 liters of blood to prime the reservoir, oxygenator, and tubing and to provide a reserve of 300 to 500 milliliters.

RESULTS

Table I shows results of the preliminary series. Hypothermia was not used in any of these experiments. Ventricular fibrillation was not induced in the first 3 dogs but developed regardless if the duration of cardiac anoxia was 10 minutes or longer. Because ventricular fibrillation was apparently inevitable and because defibrillation was no problem, deliberate use of the arrhythmia was instituted. The heart was arrested immediately without the period of contractions of diminishing amplitude which heralds anoxic arrest. The defibrillatory effort was delayed for 5 to 8 minutes after aortic disocclusion and consisted of massage and electric countershock with or without a minute dose of epinephrine. No other drugs or chemicals were used in any experiment.

The uniformity of flow rates reflects the constant use of Nos. 22 F. and 24 F. catheters in the superior and inferior venae cavae respectively. Duration of support generally exceeded the period of anoxia and approached 1 hour in dog 7. All dogs survived and were sacrificed for blood 1 to 2 weeks later.

It was clear from data in the early group that periods of anoxia longer than 20 minutes would require inordinately long support with the heart-lung apparatus. Selective cardiac hypothermia was adopted with a view to prolonging the safe period of cardiac anoxia without a concomitant increase in the duration of pump-oxygenator support. The least complicated method for inducing

TABLE III.—FORTY-FIVE MINUTES OF CARDIAC ANOXIA WITH HYPOTHERMIA OF THE HEART

No.	Weight, kgm.	Flow rate, ml./min.	Duration of machine support, mins.	Total bypass time, mins.	Ventricular fibrillation	Fate	Temperature C.° R.V.	L.V.	Body
1	13.6	1400	25	72	Induced	Long term survivor	22	25	36
2	19	1400	13	60	Induced	Long term survivor	—	—	—
3	15	1400	15	62	Induced	Long term survivor	25	28	35

TABLE IV.—ONE HOUR OF CARDIAC ANOXIA WITH HYPOTHERMIA OF THE HEART

No.	Weight, kgm.	Flow rate, ml./min.	Duration of machine support, mins.	Total bypass time, mins.	Ventricular fibrillation	Fate	Temperature C.° R.V.	L.V.	Body
1	19	1400	30	92	Induced	Long term survivor	22	29	36
2	23	1500	90	152	Induced	Died	28	31	36
3	26	1800	30	95	After 3 mins. aortic occlusion	Long term survivor	16	20	35
4	24	2000	20	85	After 5.5 mins. aortic occlusion	Long term survivor	20	28	36
5	14	1400	20	82	After 7 mins. aortic occlusion	Long term survivor	16	22	35

hypothermia of the heart seemed to be simple perfusion of the suspended pericardial sac. The following groups were submitted to varying limits of cardiac anoxia under protection of selective cooling of the heart.

Table II lists 5 dogs with cardiac anoxia of 30 minutes. Ventricular fibrillation was induced and abolished in each animal. All hearts were cooled by direct contact with saline at 0 to 5 degrees C. Pump-oxygenator support did not exceed the period of cardiac anoxia in any animal and in fact corresponded to the requirement for lesser limits of anoxia at normal heart temperature.

Again survival was routine, and since the endpoint was clearly not in the immediate area of 30 minutes of aortic occlusion, the period of anoxia was increased to 45 minutes.

Table III shows the results obtained in 3 animals with 45 minutes of cardiac anoxia. With the right ventricle uppermost in the right thoracotomy approach, myocardial temperature was predictably less diminished in the left ventricle. Fibrillation was induced in all dogs, and all survived. The period of support was no greater than in dogs with 30 minutes of cardiac anoxia. Dogs 2 and 3 required no epinephrine, but the first animal was not successfully defibrillated until 15 minutes after restoration of coronary flow: 0.5 milliliter of 1:1,000 epinephrine was used to enhance coronary arterial blood flow prior to electrical countershock.

The ease with which the last 2 dogs assumed the burden of the circulation suggested that myocardial anoxia could be extended to a full hour with expected survival.

Table IV shows the validity of this suggestion. All hearts were cooled by the local application of saline. The only dog failing to survive did not have the benefit of a left atrial catheter to prevent distention of the heart with bronchial return. Fibrillation was not induced in 3 dogs but developed shortly after occlusion of the aorta. No good evidence was found to indicate that the limits of cardiac anoxia had been reached under the conditions of this experiment. The last 2 dogs required only 20 minutes of support with the heart-lung machine, the same interval administered to dogs undergoing 15 minutes of anoxia at normal temperature.

DISCUSSION

Anoxic arrest was utilized initially by Lillehei who placed a choker around the

supravalvular aorta. The coronary circulation was intermittently suspended for the placement of a crucial stitch. Melrose adapted Sidney Ringer's original observations for elective cardiac arrest with potassium. Potassium arrest was widely used, but the uncertainty of resuscitation after more than 30 minutes of cardioplegia and the increased incidence of postoperative heart block directed attention again to simple anoxia of the heart with or without hypothermia.

Selective cooling of the heart is an attractive adjunct for anoxic arrest because of the need for abolishing coronary flow for a considerable interval of time in the surgical correction of many cardiac lesions. Surface cooling is effective and adds little to the inherent complexity of the bypass procedure. Pericardial irrigation with cold saline or other isotonic solution during anoxic arrest avoids the disadvantages of potassium arrest or coronary infusion with cold blood, yet it provides a dry, quiet heart for prolonged periods.

Of interest is the fact that the only death in any group was of an animal whose bronchial return was not removed during the perfusion by a left atrial catheter. The heart was distended but defibrillated uneventfully at the conclusion of the prescribed period of anoxia. Despite 1½ hours of extracorporeal heart-lung support, a satisfactory arterial pressure could not be maintained in the systemic circulation.

Consistent survival in the animals of this study attests to the efficiency of local hypothermia of the heart when prolonged periods of cardiac anoxia are desired. Experiments are now under way in which the duration of cardiac anoxia is necessarily protracted, and results thus far confirm the findings of this study.

SUMMARY

Selective, local hypothermia of the heart permits at least 1 hour of cardiac anoxia in the dog during cardiopulmonary bypass with blood at normal body temperature. The usual duration of pump-oxygenator support is 20 minutes after release of aortic occlusion. Decompression of the left atrium is essential to prevent cardiac distention and to provide for maximal cooling of the heart.

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PRIMARY LYMPHOSARCOMA OF THE STOMACH

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PRIMARY LYMPHOMAS of the stomach comprise between 1 and 3.7 per cent of all gastric cancers. Individual experience with these lesions is somewhat limited and Taylor, Archer and Cooper, Cameron and Breslich, Snoddy, and Jordan and associates have collected the reports of others and have added their observations. Since Taylor collected 152 cases prior to 1937, considerable interest has been shown in these tumors, and Deeb estimated in 1952 that more than 600 cases have been reported. The added interest in this type of tumor stems in part from the fact that although the 5 year survival rate reported in the literature ranges from zero to 68 per cent, it is generally considered to be far superior to that reported in carcinoma of the stomach.

Twenty-six previously unreported cases of patients with proved primary lymphosarcoma of the stomach who were treated on the Surgical and Radiological Service of the Hospital of the University of Pennsylvania between the years 1939 and 1957 inclusive are included in this report. There are 7 five year survivals of a possible 15 patients. Those patients found at the time of operation to have a generalized lymphoma have been discarded.

All patients have been followed up for a period of time varying from 6 months to 18 years.

GENERAL DATA

The general data, results, and follow-up have been tabulated in Table I. Among the 26 patients with primary lymphosarcoma of the stomach, 17 were females and 9 males. The high ratio of females is at variance with many reports. Their ages ranged from 36 to 88 years, with an average age of 61 years. The age incidence was as follows: 1 in the fourth decade, 3 in the fifth, 7 in the sixth, 10 in the seventh, 4 in the eighth, and 1 in the ninth decade of life. None were very young. Several authors reported the average age incidence in the fifth decade.

The signs and symptoms were protean. The most frequent findings (noted in 14 instances) were abdominal pain, usually epigastric but not typical from patient to patient, and ill defined weight loss varying from a few pounds to more than 35 pounds. Vomiting was recorded in 13 patients but in only 3 was there any degree of hematemesis. A palpable abdominal mass was found in 10 (Table II). The duration of symptoms varied, ranging from a few days to more than 1 year, and in 1, possibly 12 years. The usual duration of symptoms from their onset until time of operation was 5 or 6 months.

Severe anemia was not encountered frequently and was not a differential diagnostic aid. Hemoglobin levels ranged from 7.5 to 15 grams per cent with the average about 11.8 grams per cent. No abnormal white cell counts were recorded although differential counts were not done in all instances. Similar to the experience of others nothing was found in the routine work-up that would seem to suggest lymphoma of the stomach in preference to any other type of malignant neoplasm.

Roentgenologic determinations were the most useful aid in diagnosis. Roentgenograms of the upper gastrointestinal tract were made in 23 patients, and a definitive diagnosis of malignant tumor was made in

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TABLE I.—CLINICAL FINDINGS, THERAPY, AND FOLLOW-UP IN 26 PATIENTS WITH LYMPHOMA OF THE STOMACH

Pt. Age, yrs. Sex	*Clinical findings*	*X-ray findings*	*Surgery performed*	*Pathologic lymphosarcoma*	*X-ray therapy**	*Follow-up*
L.J. 36 F	Weakness, wt. loss, vomiting, hematemesis 1 yr. duration. Abd. mass, palpable	Distorted gastric rugae	Biopsy only. Lesion involved entire stomach 3–28–39	Lymphocytic cell type of stomach	3–39, 874 rads, 32 days 7–39, 978 rads, 32 days 10–39, 770 rads, 25 days 12–39, 532 rads, 13 days	Alive and well 18 yrs. postop. No evidence of disease
E.M. 69 F	Weight loss, 1 year duration	Gastric lesion probably malig.	Subtotal gastrectomy, (palliative) 7–28–43	Reticulum cell type stomach with metast. to inferior gastric lymph nodes	9–43, 216 rads, 8 days 2–46, 2064 rads, 23 days 12–47, 3154 rads, 35 days	Died 4½ yrs. postop. from hemorrhage 2° to thrombocytopenic purpura. No autopsy
E.H. 54 F	Epigastric pain, wt. loss, vomiting several mos. duration	Lesion prob. malig. in lower portion of greater curvature	Subtotal gastrectomy (curative) 12–27–43	Reticulum cell type stomach with metast. to 1 inferior gastric lymph node	10–44, 3245 rads, 72 days	Alive and well 12 yrs. postop. Recent G.I. series negative
W.J. 45 M	Epigastric pain, vomiting, wt. loss several months duration	Malignant neoplasm of stomach	Subtotal gastrectomy (curative) 3–10–44	Reticulum cell type stomach with metast. to super. and infer. gastric lymph nodes	None	Died. 2½ yrs. postop. of uremia and hypertension. Autopsy showed no evidence of recurrence
I.B.	Epigastric pain 3 mos. duration, severe anemia (9.8 gm. per cent)	Malig. lesion involving great and lesser curvatures	Subtotal gastrectomy (curative) 8–8–44	Lymphocytic cell type of stomach	10–44, 1297 rads, 14 days	Alive and well 13 yrs. postop. Abd. mass disappeared
M.M. 65 F	Epigastric distress vomiting 6 mos., wt. loss. Abd. mass.	Huge malig. involving most of stomach	Biopsy 9–13–44	Lymphocytic cell type of stomach	None	Died 2 mos. postop. No autopsy
E.B. 63 M	Epigastric pain, vomiting, wt. loss 3 mos. Abd. mass, severe anemia (9.6 gm. per cent)	Obst. series distention of small intestine	Subtotal gastrectomy (curative) 5–9–45	Reticulum cell type stomach with metast. to super. and infer. gastric lymph nodes	9–50, 2660 rads, 40 days	Died 5½ yrs. postop. Autopsy revealed extensive metastases
I.L. 49 F	Epigastric pain, 1 mo. Severe anemia (9.9 gm. per cent)	Filling defect on greater curvature. Chest x-ray. Possible mass in superior mediastinum	Subtotal gastrectomy (palliative) 6–28–49	Reticulum cell type stomach. None of 20 lymph nodes involved	12–49, 543 rads, in 13 days 2–50, 1719 rads, 57 days (to mediastinum) 2–50, 770 rads, in 57 days	Died 9 mos. postop. No autopsy. Recent chest film showed increase in size of mediastinal mass

*X-ray therapy: using parallel opposing portals, usually 15 by 16 cm., conventional apparatus was employed (200 KVP, 0.5 mm. copper and 1 mm. aluminum), dosage calculated to the midplane of the stomach.

TABLE I.—CLINICAL FINDINGS, THERAPY, AND FOLLOW-UP IN 26 PATIENTS WITH LYMPHOMA OF THE STOMACH—Continued

Pt. Age, yrs. Sex	*Clinical findings*	*X-ray findings*	*Surgery performed*	*Pathologic lymphosarcoma*	*X-ray therapy**	*Follow-up*
E.J. 53 F	Increase in abd. size, 1 yr. duration abd. mass	Filling defect in stomach	Biopsy tumor invaded gastrohepatic ligament 6–29–49	Reticulum cell type stomach with metastases in gastrohepatic omentum	8–49, 616 rads, in 34 days	Alive and well 8 yrs. postop. cholecystectomy and liver biopsy 6½ yrs. from initial surgery showed no evidence of tumor
A.R. 64 F	Abd. pain, vomiting, wt. loss 4 mos. duration	Fungating mass in distal third of stomach	Biopsy and gastroenterostomy	Reticulum cell type of stomach	5–50, 1590 rads, in 21 days	Died 2 mos. postop. No autopsy
K.D. 74 F	Vomiting 2 mos. duration. Wt. loss	Filling defect in prepyloric area	Subtotal gastrectomy (curative) 11–9–50	Reticulum cell type stomach with metastases to inferior gastric lymph nodes	11–50, 1889 rads, in 39 days	Died 3 mos. postop. No autopsy
Y.G. 70 F	Epigastric pain 2 mos. abdominal mass	Obst. series showed small bowel mechanical obst. Chest film: pleural effusion	Subtotal gastrectomy (palliative) 5–23–51	Reticulum cell type stomach with extension into the colon	None	Died 2 mos. postop. No autopsy
F.P. 68 F	Rt. upper quadrant pain and vomiting 5 mos. duration. Severe anemia (9.1 gm. per cent)	Large tumor at fundus of stomach	Subtotal gastrectomy (palliative) 10–16–51	Reticulum cell type with metastases to inferior gastric lymph nodes	10–51, 325 rads, in 8 days	Died 9 mos. postop. Autopsy showed massive pulmonary metastases
J.R. 53 F	Epigastric pain, vomiting, wt. loss 4 mos. duration	Not done	Subtotal gastrectomy (curative) 8–21–51. Lesion found at cholecystectomy	Reticulum cell type stomach	None	Alive and well 5 yrs. postop.
S.A. 51 F	Severe hemetemesis 2 wks. duration	Antral defect probably malig.	Subtotal gastrectomy (curative) 9–18–52	Reticulum cell type stomach with metastases to inferior gastric lymph nodes	None	Alive and well 5 yrs. postop. Append. 5 yrs. postop. No evidence dis.
E.S. 49 F	Vomiting, wt. loss 2 mos. duration, abd. mass (severe anemia 9.0 gm per cent)	Extensive les. of fundus, midportion and antrum	Subtotal gastrectomy (curative) with excision of omentum and section of liver 3–19–53	Reticulum cell type stomach with spread to liver and omentum	None	Alive and well 4¾ yrs. postop.
W.S. 74 M	Epigastric distress 2 mos. duration	Large polypoid ca. in body of stomach	Subtotal gastrectomy (curative)	Reticulum cell type with metastases to regional lymph nodes	None	Died 1 mo. (operative death). Autopsy showed no further tumor

*X-ray therapy: using parallel opposing portals, usually 15 by 16 cm., conventional apparatus was employed (200 KVP, 0.5 mm. copper and 1 mm. aluminum), dosage calculated to the midplane of the stomach.

TABLE I.—CLINICAL FINDINGS, THERAPY, AND FOLLOW-UP IN 26 PATIENTS WITH LYMPHOMA OF THE STOMACH—Continued

Pt. Age. yrs. Sex	*Clinical findings*	*X-ray findings*	*Surgery performed*	*Pathologic lymphosarcoma*	*X-ray therapy**	*Follow-up*
E.P. 65 F	Abdom. pain, 1 yr. duration. Marked wt. loss	Linitis plastica of distal half of stomach	Subtotal gastrectomy (curative) 7–7–53	Reticulum cell type with metastases to regional nodes	None	Alive and well 4½ yrs. postop. Recent G.I. and chest films negative
D.G. 67 M	Epigastric pain 3 mos.	Lesion on greater curvature prob. malignant	Subtotal gastrectomy (curative) 5–8–54	Lymphocytic cell type	None	Alive and well 3½ yrs. postop.
J.C. 88 M	Wt. loss, epigastric distress, pres. abdominal mass	Large lesion on lesser curvature probably malig.	Biopsy and gastrojejunostomy 6–4–54	Reticulum cell type stomach	6–54, 1398 rads in 23 days	Died 8 mos. Liver metast. at autopsy
J.L. 60 M	Heartburn and tarry stools 6 mos. duration. Recent hematemesis	Lesion of stomach probably malignant	Subtotal gastrectomy (curative) 10–26–54	Probable plasmacytoma of stomach	11–54, 2572 rads in 43 days	Alive and well 3 yrs. postop.
M.D. 72 F	Epigastric pain, vomiting, wt. loss 3 mos. duration	Extensive ulcerated mass in gastric antrum	Subtotal gastrectomy (curative) 11–4–54	Reticulum cell type of stomach	None	Alive and well 3 yrs. postop.
F.S. 54 M	Epigastric pain, weakness, anorexia, wt. loss 1 yr. duration, recent vomiting	Probable malignant lesion of stomach	Total gastrectomy (curative) 4–13–57	Reticulum cell type of stomach	None	Alive and well 6 mos. postop.
S.S. 65 M	Postprandial discomfort 1 mo. Abdominal mass	Large cancer of fundus	Biopsy only 4–29–55	Reticulum cell type	6–55, 1639 rads, 35 days 6–55, 599 rads (lower abd.) 35 days	Died in 3 mos. No autopsy
A.K. 75 F	Abdominal mass 1 mo. duration	Unsatisfactory due to residue in stomach	Subtotal gastrectomy (curative) 10–15–55	Reticulum cell type with metast. to regional lymph nodes	None	Alive and well 3 mos.
T.A. 66 M	Loss of appetite 3 mos. duration	Malignant lesion of stomach	Subtotal gastrectomy (palliative) 11–15–50	Reticulum cell type with metastases	2–51, 1531 rads 21 days	Died 30 mos. postop. metastases to lungs and pleura at autopsy

*X-ray therapy: using parallel opposing portals, usually 15 by 16 cm., conventional apparatus was employed (200 KVP, 0.5 mm. copper and 1 mm. aluminum), dosage calculated to the midplane of the stomach.

18. A filling defect was noted in 3 others; 1 showed distorted gastric rugae; and 1 examination was unsatisfactory because of retained food.

A diagnosis of a malignant neoplasm was made in 24 cases preoperatively either by roentgenologic examination (18 cases), by the presence of a palpable mass (5 cases), or by a filling defect on the greater curvature and an associated mediastinal mass (1 case). The last patient (I. L.) was thought to have a primary reticulum cell lympho-

sarcoma with a single metastasis in the mediastinum. In 2 patients the diagnosis was made at operation. In 1 of these the lesion was found by exploration of the abdomen at the time of cholecystectomy (J. R.) and in the other by exploration for intestinal obstruction (Y. G.). In the latter the gastric lesion was found to have infiltrated the transverse colon causing the intestinal obstruction. In our series the surgeon could be reasonably confident that he would be dealing with a malignant tumor in 24 of 26 cases but in none was the preoperative diagnosis lymphosarcoma.

At laparotomy a majority of the tumors were diagnosed as lymphomas by their clinical appearance or by frozen section. If the lesion was judged by the surgeon to be inoperable, only a biopsy or palliative type of procedure was performed. Included in this group were 4 biopsies, 2 biopsies combined with gastroenterostomy, and 5 palliative gastric resections. In 15 cases a curative type of gastric resection was carried out. A curative procedure included those cases in which, in the judgment of the surgeon, all visible tumor was removed. The general policy was to perform a Hofmeister subtotal gastric resection (of about 75 per cent of the stomach) with wide excision of the gastrohepatic and gastrocolic ligaments.

There was 1 operative death in the series. This occurred in a 74 year old male who had a curative gastric resection. His gastrojejunal anastomosis broke down, and a draining fistula developed which failed to heal despite a jejunostomy. Bronchopneumonia was the cause of death 30 days after his initial operation. At necropsy there was no evidence of tumor in the gastric remnant although there were a few bizarre appearing cells in the inferior gastric lymph nodes.

In this presentation, reticulum cell sarcoma, lymphosarcoma, and plasmacytoma are studied as a group. The histogenesis and thus relationship of these lesions are open to debate although many pathologists agree that lymphosarcoma and reticulum cell sarcoma, at least, represent variants of a single basic neoplastic process. Only 4 of our cases were considered examples of lymphocytic cell type lymphosarcoma. One case was a plasmacytoma. One case originally classified as Hodgkin's disease was on review considered to be a reticulum cell sarcoma, and the remaining cases were all reticulum cell sarcoma, by far the most common of the various malignant lymphomas (21 cases in all).

TABLE II.—DIAGNOSIS

Findings	*No. of cases*
"Malignant neoplasm" (found on g.i. series)	18
Abdominal pain	14
Weight loss	14
Vomiting	13
Abdominal mass	10
Hemoglobin of less than 10 grams per cent	6
Hematemesis	3
Incidental finding at cholecystectomy	1

The gross appearance of these lesions has been well described by Stout and our cases fit closely. The infiltrate of abnormal cells arises in the mucosa or submucosa forming a thick plaque or disc-like tumor usually sharply elevating the mucosa and usually with 1 or several shallow or deep ulcerations more or less central to the disc. Occasionally, the major portion of the lesion is ulcerated with surrounding raised rolled edges closely resembling ulcerative carcinoma or less commonly a large peptic ulcer. The muscle coat may be intact or more or less thickened by infiltrate, and similarly large nodulation of tumor may appear on the serosa. Occasionally, superimposed peptic ulceration may destroy muscle in the base of the ulcer but we have not seen the muscle coat completely replaced by tumor as occurs in lymphomas of the small bowel. The adjacent lymph nodes, if involved, are large, firm, and homogeneous but lack the hard consistency of metastatic carcinoma.

In the literature a form of superficial submucosal infiltrate producing giant rugae is described. None of our cases had this appearance.

Fourteen patients received a postoperative course of radiation therapy directed to

TABLE III.—DURATION OF SURVIVAL IN MONTHS

	With no radiation		Radiation	
	Survival, mos.	*Median survival, mos.*	*Survival, mos.*	*Median survival, mos.*
Male	1, 6*, 30, 42	18	3, 6, 30, 36*, 66	30
Female	1, 3, 24, 36*, 48*, 57*, 60*, 60*	42	2, 3, 9, 9, 57, 96*, 144*, 156*, 216*	57
Positive nodes	1, 1, 3, 6*, 30, 57*, 48*, 60*	18	2, 3, 3, 6, 9, 30, 57, 66, 96*, 144*, 216	30
Negative nodes	24*, 36*, 42*, 60*	39	9, 36*, 156*	36
Curative resection	1, 6*, 24*, 30, 36*, 42*, 48*, 57*, 60*, 60*	39	3, 36*, 66, 144*, 156*	66
Palliative or biopsy	1, 1, 3	1	2, 3, 6, 9, 9, 30, 57, 96*, 216*	9

*Living.

the stomach and its bed. The treatment generally was begun within the first month following the operative procedure. Conventional x-ray therapy techniques were used: 200 kilovolts pressure, 15 milliamperes, 1.0 millimeter aluminum and 0.5 millimeter copper with a half value layer of 1.3 millimeters copper, and a 50 centimeter target skin distance. The portals were parallel opposing and usually measured 15 by 16 centimeters. A median calculated dose of 1,464 rads was given to the midplane of the stomach in a median time of 33 elapsed days (see Table I).

Of the 14 patients, 2 required retreatment to the primary lesion, and 3 required simultaneous or subsequent treatment to areas which were thought to be metastases from the primary gastric lesion.

RESULTS

In Table III the duration of survival of all the patients with primary lymphosarcoma of the stomach with respect to x-ray therapy is presented. It is not apparent why women have had a longer survival in our series.

TABLE IV.—FOLLOW-UP OF 5 YEARS OR MORE IN 15 CASES

	Survival in months	*Median survival, mos.*
Living (7 cases)	216,144,156,66,96,60,60	81
Dead of disease	22,2,3,9,9,57	3
Dead of other causes	30	30

In the group in which operation alone was performed and the pathologic specimen showed positive nodes, the median survival was 18 months. If a similar group with positive nodes received postoperative radiotherapy, the median survival was increased to 30 months. If the surgical specimen showed negative nodes and no further definitive therapy was carried out, the median survival was 39 months; whereas it was 36 months if the similar group had postoperative radiation therapy.

The most interesting finding is seen in the correlation of survival with curative resection. When a curative surgical procedure alone was performed, the median survival was 39 months. If a similar group received postoperative radiation therapy, the median survival was 66 months. In the group of 15 patients who had curative resections 11 are living, apparently free of their disease, from 6 months to 12 years after resection for lymphosarcoma of the stomach. There have been 4 deaths, 1 of which was operative. The other 3 died at 3 months, 2½ years, and 5½ years after the resections, presumably of their disease.

It, therefore, appears that postoperative radiation therapy is not indicated in that group of patients in which a curative procedure is performed and the surgical specimen reveals nodes negative for tumor. On the other hand, it appears to be definitely indicated when the surgical specimen re-

veals nodes positive for tumor. There is little question of the value of postoperative radiation therapy when only a biopsy or a palliative procedure was carried out.

It is interesting to note that there are 2 long term survivors in the group in which biopsy only was performed at the time of laparotomy. Both had postoperative irradiation. These patients are living and symptom-free, 18 and 8 years after biopsy and irradiation. The other 4 patients, who had only a biopsy, died at 1, 2, 3, and 6 month intervals following laparotomy. There appeared to be no correlation with type of tumor and survival, although it is to be noted that the majority of the patients had reticulum cell type.

Fifteen patients of the group have been followed up for 5 years or more (Table IV). Seven are living and apparently free of their disease. Five of the 7 patients who underwent curative resections during this time are included in this group. Two of the 5 year or longer survivors had biopsy only, followed by radiation (Table I).

SUMMARY

1. Twenty-six cases of primary lymphosarcoma of the stomach seen at the Hospital of the University of Pennsylvania in the period from 1939 through 1957 are presented.

2. The method of treatment has been discussed with particular reference to subtotal gastric resection and postoperative irradiation.

3. Postoperative radiotherapy is indicated in those cases in which a curative procedure was done and the surgical specimen showed nodes involved with tumor.

4. Postoperative radiotherapy is indicated in those instances in which only a biopsy or a palliative procedure was performed.

5. Two patients, found to be inoperable, survived longer than 7 years when treated by irradiation following a biopsy at the time of operation.

6. Seven 5 year survivals following treatment for lymphosarcoma are presented.

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THE EFFECT OF OPERATIVE TRAUMA ON THE GASTROINTESTINAL ABSORPTION OF FAT

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THE METABOLIC RESPONSE to operative trauma involves to some extent every system of the body. Participation by many neuroendocrine structures—adrenocortex and adrenomedulla, thyroid, pituitary—is well established by study of blood hormone levels and alterations in the composition of body fluids. The role of the pancreas and the reproductive endocrines is not clear.

A convenient method for study of pancreatic function and gastrointestinal absorption is the oral administration of capsules containing radioactive iodine labeled triolein or oleic acid. Oleic acid is absorbed without the action of enzymes since degradation into absorbable components is unnecessary. Triolein, on the other hand, requires fat splitting enzymes, chiefly pancreatic lipase for transformation into an absorbable form. Subsequent determination of the radioactivity of blood samples reflects the amount of absorption of the fat. The value of this method as a differential diagnostic measure in suspected pancreatic and gastrointestinal malabsorption syndromes is well established.

If pancreatic lipase activity is altered as a part of the metabolic response to trauma, triolein absorption should vary in the postoperative period as compared to the preoperative period. On the other hand, oleic acid absorption should remain unchanged. If gastrointestinal absorption of fat *per se* is altered, variation after operation of absorption of both triolein and oleic acid would be anticipated. The present study was designed to evaluate the possible role of the pancreas in the total response to extra-abdominal, major operative trauma by use of radioactive iodine labeled fat.

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MATERIALS AND METHODS

Thirty-nine patients undergoing major, extraperitoneal operation were studied. The patients were divided into two groups: 20 patients received radioactive iodine labeled triolein and 19 patients, labeled oleic acid. All degrees of operative trauma were included ranging from hemorrhoidectomy to pneumonectomy. The main prerequisite for admission into the study was the ability of the patient to take oral nutrition prior to and immediately after operation. Patients ranged in age from 16 to 89 years and preoperatively were in varying clinical states of well-being. Both groups were homogeneous in so far as sex, age, operation, and preoperative status were concerned. General and spinal anesthesias were represented in each group. No patient had known gastrointestinal or endocrine disease. Each patient acted as his own control since he was studied before and after operation in precisely the same manner.

Twelve hours prior to starting the study each patient received 4 milliliters of Lugol's solution orally to flood the body with iodine to prevent thyroid trapping of the radioactive iodine to be administered later. This precaution recently has been demonstrated by Grossman and Jordan to be unnecessary.

Twenty-four hours before operation and 18 to 24 hours after operation each patient received a capsule containing a known amount of radioactive triolein or oleic acid. The dose varied from 6 to 50 microcuries. The capsule was given orally after a fasting

TABLE I.—TRIOLEIN

Patient Sex Age	Preop. condition	Operation	Anesthesia	Uptake I^{131}, per cent dose per liter — Preoperative 2 hr.	Preoperative 4 hr.	Preoperative 6 hr.	Postoperative 2 hr.	Postoperative 4 hr.	Postoperative 6 hr.
1 M 70	Fair	Pneumonectomy	General	0.3	1.0	1.0	0.1	0.1	0.1
2 F 57	Good	Segmental resect. lung	General	1.0	1.1	0.8	1.5	1.6	1.6
3 F 55	Fair	Bilobectomy	General	0.8	2.5	2.6	0.2	0.2	0.2
4 F 17	Good	Exc. mediast. tumor	General	1.4	2.1	1.7	0.3	0.4	0.4
5 F 75	Fair	Extended simple mastectomy	General	1.7	2.5	2.6	2.6	2.0	1.9
6 F 58	Fair	Radical neck dissect.	General	1.7	—	2.4	0.2	0.2	0.2
7 M 55	Fair	Pneumonectomy	General	1.5	2.1	3.5	0.1	0.1	1.8
8 F 56	Fair	Wedge resection lung	General	1.6	1.6	2.3	0.9	0.7	1.0
9 M 56	Fair	Decortication lung	General	1.1	2.3	2.3	1.7	2.2	1.2
10 F 70	Poor	Simple mastectomy	General	0.2	3.7	2.6	1.1	2.0	2.7
11 M 67	Poor	Hernia repair	General	0.3	0.5	1.3	0.1	0.9	1.1
12 F 89	Poor	Hip pinning	General	0.2	0.9	1.0	0.1	2.5	3.2
13 M 61	Poor	Explor. thoracotomy	General	1.5	1.6	1.4	0.6	1.2	1.4
14 F 80	Poor	Hip pinning	General	2.8	3.7	3.0	1.7	1.7	2.4
15 F 88	Poor	Hip pinning	General	0.5	0.6	0.9	0.1	0.1	0.1
16 M 38	Good	Hernia repair	General	0.8	0.9	1.0	0.5	1.3	1.5
17 M 55	Good	Hernia repair	Spinal	0.5	2.5	4.2	0.2	2.0	3.3
18 M 60	Poor	Hernia repair	General	0.4	1.0	1.6	0.2	0.5	0.6
19 F 49	Good	Reduction patella fracture	General	2.3	2.2	2.2	0.1	1.0	1.2
20 F 37	Good	Hemorrhoidectomy	Spinal	0.5	2.6	2.6	2.2	1.6	1.9

TABLE II.—OLEIC ACID

Patient Sex Age	Preop. condition	Operation	Anesthesia	Uptake I^{131}, per cent dose per liter — Preoperative 2 hr.	Preoperative 4 hr.	Preoperative 6 hr.	Postoperative 2 hr.	Postoperative 4 hr.	Postoperative 6 hr.
1 M 16	Good	Hernia repair	Spinal	0.3	1.7	1.4	0.8	1.2	1.3
2 M 72	Good	Hernia repair	Spinal	2.8	2.5	2.2	3.0	2.7	2.6
3 M 67	Fair	Hernia repair	Spinal	2.8	2.6	2.2	2.4	2.4	2.7
4 M 80	Fair	Hernia repair	General	2.4	2.1	1.8	2.5	2.4	2.1
5 F 38	Good	Skin graft to leg	General	2.1	1.9	1.6	2.4	2.0	1.5
6 M 70	Good	Excis. fistula-in-ano	Spinal	3.2	2.1	2.4	2.8	3.1	3.1
7 F 58	Good	Reduction patella fracture	General	4.2	4.6	3.6	2.5	—	2.6
8 M 73	Fair	Skin graft to foot	Spinal	2.2	2.0	1.7	1.2	2.1	1.6
9 F 34	Good	Radical mastectomy	General	2.9	3.1	3.0	3.1	2.8	2.6
10 M 44	Good	Lobectomy	General	1.7	1.5	1.5	0.3	1.1	1.6
11 M 47	Good	Lobectomy	General	2.7	2.6	2.2	1.4	1.7	1.3
12 F 41	Fair	Cup arthroplasty hip	General	2.4	2.6	2.3	2.5	1.8	1.7
13 M 20	Good	Exc. mediast. tumor	General	2.3	2.1	1.6	0.1	0.1	0.1
14 F 81	Poor	Hip pinning	General	3.6	3.7	3.4	3.5	3.8	3.6
15 M 56	Poor	Explor. thoracotomy	General	3.0	2.2	1.6	0.1	0.5	1.4
16 M 76	Poor	Hip pinning	General	3.8	3.0	2.7	4.3	4.3	4.5
17 F 62	Poor	Thoracoplasty	General	2.3	2.1	2.3	2.8	2.5	2.1
18 M 75	Poor	Explor. thoracotomy	General	2.5	2.8	2.4	4.0	3.4	2.4
19 M 69	Poor	Skin graft to trunk	General	2.1	2.1	1.5	2.4	1.6	1.6

period (at least 6 hours) accompanied by 150 milliliters of ginger ale to hasten gastric emptying. Heparinized blood samples were drawn at 2, 4, and 6 hours after administration of the capsule and radioactivity of whole blood (1 milliliter) determined in a scintillation well detector. The percentage uptake of the administered radioactive iodine per liter of whole blood was then calculated by comparison with a standard reference solution. Corrections were made in the postoperative determinations for residual radioactivity from the preoperative study. Whole blood was analyzed since it has been demonstrated by Grossman and Jordan that this is as efficient, if not more efficient, for determination of uptake of radioactive fat as more complex methods utilizing plasma or the lipid fraction of plasma. Studies of fecal radioactivity were not feasible in this study because of the brief time lapse between the two administrations of the radioactive fat.

RESULTS

A statistically significant depression was found in the uptake of triolein in the postoperative period while oleic acid uptake was unchanged. Tables I and II list the crude data in each group of patients. Table III details the calculated significant deviation ("t") of the data from the true mean. The 2 hour triolein data fall slightly short of significance while the 4 and 6 hour data are highly significant. The oleic acid data lack significance beyond chance.

DISCUSSION

The details of site and mechanism of absorption of fat from the gastrointestinal tract are uncertain. The small bowel, especially the distal portion, is probably the area of greatest absorptive activity. It is clear that bile salts and pancreatic lipase are necessary for neutral fat absorption. The bile salts act to emulsify fats so that lipase contact is increased. How much bile is required to achieve complete lipase degradation of neutral fat into monoglycerides, fatty acids, and glycerol prior to absorption is unknown. In all likelihood there is normally a great surplus present over basic needs.

TABLE III.—DIFFERENCES BETWEEN PREOPERATIVE AND POSTOPERATIVE UPTAKE OF TRIOLEIN AND OLEIC ACID 2, 4, AND 6 HOURS AFTER INGESTION

The measurement used is the ratio of the mean difference to the standard error of the mean ("t" value).

	2 hr.	*4 hr.*	*6 hr.*
Triolein	1.94	4.11	3.88
Oleic acid	1.50	0.77	1.47

Significance established 5 per cent level at 2.09 and 1 per cent level at 2.86 (triolein).

Significance established 5 per cent level at 2.10 and 1 per cent level at 2.88 (oleic acid).

CALCULATIONS

n = Number of blood samples

X = Difference (preoperative-postoperative) I^{131} uptake of blood samples

M = Mean of differences (X)

V_1 = Variance individual values

V_2 = Variance of mean of differences (M)

SE = Standard error of mean

t = Significant deviation from true mean of difference

$$V_1 = \frac{\sum (X-M)^2}{n-1}$$

$$V_2 = \frac{\sum (X-M)^2}{n(n-1)}$$

$$SE = \sqrt{V_2}$$

$$t = \frac{M}{SE}$$

Participation of the gastrointestinal tract in the total response to trauma has been studied in fragmentary fashion in the past. Hardy demonstrated that the volume of gastrointestinal secretions (probably including the pancreatic contribution) may be decreased in the posttrauma period. He has also shown that forward propulsion of bowel contents continues even in the absence of audible peristalsis. Howard reported that after trauma of war wounds gallbladder function as demonstrated by cholecystographic techniques is abnormal (3), and further that absorption of deuterium oxide (heavy water) from the gastrointestinal tract may be delayed (4).

It would appear then that there are many factors which could influence the absorption of fat after operation, any or all of which might affect the results found in the present study. Ideally, evaluation of indi-

vidual factors would require study of each patient with triolein and oleic acid during separate traumatic experiences. The impracticality of this situation is obvious. The next best method would be to study with each of the fat preparations groups of patients as homogeneous as possible as was done here.

Application of the previously mentioned known posttraumatic gastrointestinal tract alterations to the present study is necessary. Certainly if the volume of secretions (including those of the pancreas) is depressed after trauma, the amount of lipase available for triolein breakdown would be less. This could account for the depressed postoperative uptake of the radioactive iodine labeled fat. Also a decrease in the available bile salts as could result from abnormal gallbladder function could contribute to the lowered triolein absorption by providing inadequate substrate for complete lipase activity. If absorption per se were abnormal, both triolein and oleic acid absorption after operation would be depressed which was not the case here. Thus, it would appear that decreased pancreatic lipase production may be part of the general depression of gastrointestinal secretion volume perhaps associated with decreased bile salt availability after operation. This assumption could account for the significant decrease in triolein absorption after operation in the present study. A less likely possibility is a direct suppression of pancreatic activity as the result of trauma. Such a premise would be difficult to demonstrate.

SUMMARY

A decreased uptake of radioactive labeled triolein has been demonstrated to be present after extraperitoneal, major operative trauma. Oleic acid uptake under the same study conditions was unchanged. This observation suggests a decrease in pancreatic activity perhaps associated with decreased bile salt availability as part of the total body response to trauma.

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EDITORIALS

THE CAUSE FOR VISUAL AORTIC VALVULOTOMY

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AORTIC VALVULAR DISEASE, whether congenital or acquired, is one of the more frequently encountered types of cardiac deformities. For this reason, considerable interest and effort have been expended in an attempt to devise procedures for its relief.

Initial techniques employed the insertion of a dilating instrument either through the left ventricle or retrogradely, through an appendage sutured to the aorta to split the valve. Both of these procedures are still used at the present time. However, these methods are "blind procedures" and violate one of the cardinal surgical principles—that of operating under direct vision whenever possible. Before the development of a satisfactory pump oxygenator or hypothermia, these techniques were permissible and indeed lifesaving, but there seems little reason to employ them since the advent of the pump oxygenator. One of the indications for abandoning these methods is the fact that there is frequently inadequate opening of the valve with these procedures, as shown by postmortem examination. There is usually one, sometimes two, and occasionally three commissures open in the acquired stenotic valve. In addition, the valve leaflets are frequently thickened and stiff and do not function satisfactorily even if the commissures are split. A dilating procedure for the congenitally stenotic valve often produces a tear through one of the valve cusps resulting in significant aortic insufficiency. The enlarged strained left ventricle is frequently irritable and its degenerate consistency makes hemorrhage a real hazard. The transventricular method does have the advantage that it can be rapidly executed. The retrograde procedure through the appendage, as opposed to the transventricular approach, allows one to palpate the valve to determine the degree of opening but has the disadvantages of presenting a more difficult exposure. Furthermore, it is more tedious to execute and presents the possibility of hemorrhage from an often thin and degenerated aortic wall.

As visual methods have developed, it has become apparent that the valve can be opened more completely and more accurately. This is especially true of congenital aortic stenosis in which the cusps are supple and thin. The residual commissures are usually well defined. When properly opened, the valve can be restored to normal function and frequently to normal appearance.

During the past 3 years or so, patients with congenital stenosis have been operated upon in our clinic by using an open procedure. Initially, hypothermia and venous inflow occlusion were used but the time limitations imposed by hypothermia made utilization of the pump oxygenator more desirable so that it is routinely employed for this procedure.

The configuration of the aortic valve with acquired stenosis is variable, but when cal-

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cification is present, which is usually the case, considerable deformity results. It is obvious that, in order to achieve the greatest opening of such a valve without resultant insufficiency, a careful individualized valvulotomy must be performed. The only means of achieving a proper opening is to expose the valve itself adequately. In some instances, when incising the third commissure might result in considerable insufficiency, it is necessary to create a bicuspid valve. This is especially true when two of the cusps have been contracted by cicatrization and calcification and have lost the cusp-like configuration which prevents their falling back into the left ventricular chamber during diastole. In many instances, however, a tricuspid valve can be formed.

Of considerable importance is the removal of as much calcium as possible from the valve leaflets. Occasionally, a plane exists similar to that found when one performs an endarterectomy of a major artery, facilitating removal of these calcium deposits. In our experience, however, this has been the exception rather than the rule. Even if a true plane cannot be found, calcium can be removed in many cases resulting in a much thinner, more supple valve leaflet. On the other hand, calcific replacement of the valve leaflets may be so massive as to prevent the accomplishment of a satisfactory procedure on the valve. When this has occurred, a portion of or all of the valve has been replaced with a subcoronary valve prosthesis of compressed polyvinyl sponge or teflon fabric. The development of heart valve replacements has not yet been refined to the extent that they can be used routinely for replacement, however, and every effort should first be made to utilize the patient's own tissues before resorting to a synthetic material.

Of prime importance during open operations on the aortic valve is the use of coronary artery perfusion to maintain the blood supply to the heart. Perfusion of both coronary arteries is difficult and requires the use of much more apparatus in an already small operative field. Perfusion of only the left coronary artery will suffice to maintain an adequate blood flow to the heart and allows operating time in excess of 2 hours if needed. Without perfusion, cardiac contractions are often difficult to reinitiate. The same may be said for potassium citrate cardioplegia. This is especially true if insufficiency, which may accompany stenosis, has not been completely corrected.

The present series in which the pump oxygenator was used for correction of aortic stenosis is not so large as the one in which closed methods were employed but the mortality rate is nonetheless definitely lower. This factor, in combination with the other circumstances which have been pointed out, makes open valvulotomy the procedure of choice.

LETHAL FACTORS IN INTESTINAL OBSTRUCTION

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THE FIRST HALF of the twentieth century has witnessed a sustained decrease in the mortality rate of intestinal obstruction. Most of this improvement has been obtained in the management of simple obstruction. The mortality rate for strangulated intestinal obstruction remains high, in fact, it is difficult to find a series in the literature in which this figure is below 30 per cent. Mechanical occlusion of the bowel lumen with subsequent retrograde flow of intestinal contents can deprive the body of tremendous quantities of fluid in relatively short periods of time. Tissue dehydration along with severe contractions of the blood volume can well terminate fatally if allowed to go uncorrected. Serious electrolyte loss or imbalance is not uncommon especially in high obstruction. The danger of severe acid-base imbalance of the blood and tissue is recognized by all familiar with surgery as practiced today. The ill effects of advanced intestinal distention of extended duration are well documented. Increased pressure upon the intestinal wall is reflected in venous congestion since the intraluminal pressure of these vessels is less than that of accompanying arteries. Prolonged circulatory stasis with anoxia and necrosis leads to perforation of the bowel wall following which the peritoneal cavity is flooded by the highly lethal intestinal contents. The foregoing pathophysiologic manifestations are common to both simple and strangulated obstruction. Rapid blood loss of moderate to severe proportions is usually seen only in strangulated intestinal obstruction. This factor is of major concern following such vascular accidents as mesenteric venous thrombosis. Large portions of the circulating blood volume may be sequestrated, particularly, if long segments of bowel are involved. Blood loss may also result from lesions such as strangulated hernia when the neck of the sac exerts increasing pressure upon the intestinal segment. Since the venous pressure is less than the arterial the former vessels become occluded. Blood continues to flow into the involved segment of bowel but is unable to return to the circulation. Depending upon the length of bowel involved, blood loss may vary from small amounts to quantities large enough to produce shock and death.

The various deviations from the normal, as discussed before, do not relate the entire problem as far as the lethal issue of strangulation obstruction is concerned. Following the creation of a short, closed loop of strangulated ileum a rapid downhill course with death is always the case. Administration of blood, fluids, or electrolytes or the institution of nasogastric suction in no way alters the final outcome. If the segment of strangulated bowel is placed in a plastic bag so that peritoneal exposure is prevented, the animal's life is indefinitely prolonged. After 24 hours the plastic bag is found to contain dark fluid which has a foul odor. This material is lethal in amounts as small as 2 cubic centimeters per kilogram when given either intravenously or intraperitoneally to normal dogs. One animal produces enough of this fluid to kill 7 dogs of equal size. The conclusion that this material plays a major role in the lethal issue of strangulation obstruction cannot be escaped. What component of strangulation fluid is responsible for its toxic properties? It has been suggested that altered hemoglobin pigments may represent the toxic fraction. When the fluid was centrifuged at 17,000 revolutions per minute for 10 minutes the supernatant fluid was not toxic while the centrifugate gave lethal results following

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injection into normal animals. The nontoxic supernatant fluid retained the dark red color which results from hemoglobin pigments while the toxic centrifugate was almost white, indicating the absence of pigments. Strangulation of the stomach resulted in fluid ranging from low to no toxicity. If hemoglobin pigments are responsible for the toxicity of the fluid, then stomach fluid should be just as toxic as ileal fluid.

In another series of experiments 20 normal dogs were divided into two equal groups. A 10 centimeter segment of ileum was dropped into the peritoneal cavity of each animal. In the first group all the blood was washed from the ileal segment by injecting saline through the divided artery. The animals of group 2 received ileal segments which were thoroughly filled with blood by occlusion of the vein about 15 minutes before the artery was divided. There was no difference in the survival rate of the two groups of animals. Thus there is no apparent indication that hemoglobin pigments have any responsibility for the toxicity of the fluid.

It has been suggested that exotoxins or other chemical substances are responsible for the lethal properties, but passage of the fluid through a Seitz filter which removes only particles as large as bacterial cells renders the fluid nontoxic. Centrifugation at speeds mentioned could not be expected to remove molecules of a toxic substance from a true solution. A smear of the toxic centrifugate reveals many bacterial cells. If bacteria are responsible for the toxicity of the fluid then it should be possible to obtain nontoxic fluid from a segment of strangulated bowel which has been filled with an antibiotic. Both neomycin and chloromycetin were effective in eliminating the toxic properties of the resulting strangulation fluid. Antibiotics are the only substances found thus far which will protect an animal against an otherwise lethal dose of toxic strangulated fluid. Again, if bacteria are responsible for the lethal properties of strangulation fluid then stomach fluid should be less toxic than colon fluid. Following strangulation of various segments of the gastrointestinal tract the toxicity of the resulting peritoneal fluid was found to increase from the stomach to the colon. Up to 4 hours after peritoneal exposure to toxic fluid bacteria may be cultured in increasing numbers from the portal and femoral blood. Normal animals may be immunized against an otherwise lethal dose of strangulation fluid by weekly injections of small amounts of this material into the peritoneal cavity. Fluid derived from an antibiotic treated segment of strangulated bowel was not effective in creating immunity to toxic fluid. These studies indicate that bacterial cells or their endotoxins play an important role in the lethal outcome of strangulated intestinal obstruction. Improvement in the survival rate of this condition will probably accompany the acceptance of this fact along with the judicious application of appropriate therapeutic measures.

THE SURGEON AT WORK

MODIFIED OSTEOTOMY OF THE TIBIA

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A MODIFIED OSTEOTOMY of the tibia is described for the correction of both tibial torsion and bowing using the same operative site and by means of the same bone cuts. This procedure is a modification of that described by O'Donoghue.

It was undertaken first on an adolescent female for severe internal tibial torsion and outward bowing of the tibia due to vitamin D resistant rickets. Figures 1 and 2 show the appearance of the tibial shaft before and after correction following the osteotomy. Rotation and lateral bowing of the bone have been corrected.

Figure 2, in the posterior view, shows that the gap in the bone is posterior with the base of the triangle proximal, after correction of both bowing and torsion.

The amount of wedging is determined preoperatively by roentgenograms. The amount of tibial torsion that requires correction is determined clinically at the time of operation.

The surgical approach is through an anterior medial curved incision of approximately 3½ inches in length with the proximal end of the tibial shaft completely stripped of periosteum from the level of the tibial tubercle and extending distally approximately 3 inches.

After completion of the osteotomy the tibia is fixed by means of 2 stainless steel screws, and the wedge of bone removed anteriorly is not discarded but is used as multiple onlay grafts along both the lateral and medial sides of the transverse cuts. This latter detail was not included in the diagrams for the sake of simplicity.

The deformity in a 16 year old white female, preoperatively, with vitamin D resistant rickets is shown in Figure 3. The postoperative roentgenographic appearance can be seen in Figure 4. Figure 5 shows healing 9 months after operation, and further x-ray examination elsewhere more than a year later revealed maintenance

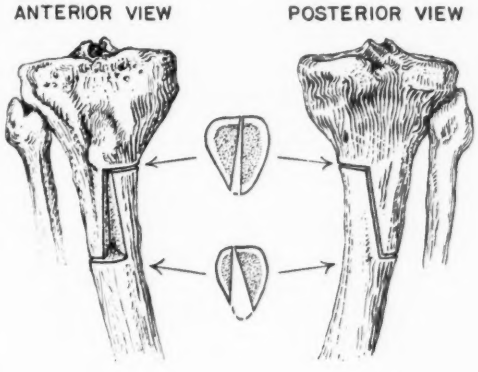

FIG. 1.

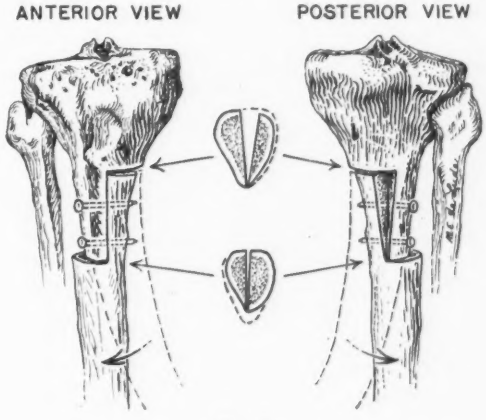

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 6.

FIG. 7.

FIG. 8.

FIG. 9.

of the correction. In Figure 6 the preoperative deformity in a 9 year old white female due to achondroplasia is visible. Figure 7 shows correction after cast removal, 2 months later. Bilateral deformities in a 12 year old white female due to achondroplasia are seen in Figure 8. Figure 9 shows complete healing with correction 3 months after operation.

SUMMARY

A rather simple, modified rotational wedge osteotomy is described which has been found to be effective in the few cases in which it has been used.

Although, in the cases illustrated, it did not seem necessary to perform osteotomy upon the fibula at the time of operation it probably would have been more physiologic to have done so. The amount of bone removed anteriorly and its shape, of course, depends upon the amount of correction which is required.

In the cases presented, particularly the last 2, in which the deformities were severe, correction was satisfactory. It is my opinion that the modified rotational osteotomy would be best for correction of very severe idiopathic outward bowing and rotational torsion of the tibia in which instances conservative treatment has not been adequate.

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THE SIGNIFICANCE OF IN VIVO MEASUREMENT OF THE COMMON BILE DUCT

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In 1931, John Deaver, who had been an active participant in the surgical progress of the biliary tract for half a century, had this to say about the common bile duct: "in retrospect, on contemplation of the good and evil in this special field of surgery, there stands out with the prominence of indelible memory, the role of the common duct. It requires much bitter and trying experience adequately to appreciate the importance of the common duct in the satisfactory and unsatisfactory results of the surgery of the biliary tract. Unlike the gall bladder, the common duct is indispensable yet it is so readily affected by disease and operative trauma, the consequences of which are often disastrous, that its surgical importance scarcely can be overestimated."

These sentiments remain applicable today despite considerable advances in surgery of the biliary tract. Excluding operative trauma, which may occur in the hands of the most expert surgeon, there are inherent potential complications of choledochotomy, such as bile extravasations around T tubes with pericholedochitis and stricture or inflammatory pressure on the duodenum, cholangitis, pancreatitis, and, more rarely, hemorrhage. In the experience of seasoned investigators, choledochostomy, when added to cholecystectomy, tripled the mortality, whether stones were found in the duct or not. On the other hand, it should be mentioned that in at least one large clinic the mortality was not significantly increased when choledochostomy was added to a cholecystectomy. The reason for this may be that in this series a large number of elective patients coming from a wide surrounding territory were included; there was thus a proportionate reduction of the more seriously ill patients who could not travel.

Fairly complete agreement exists regarding the indications for exploration of the common duct: palpable stone, dilated duct, thickened wall of duct, gallbladder containing small stones plus the presence of a large cystic duct, and a history or the presence of jaundice. Despite this agreement of indications, there is, apparently, disagreement on the interpretations of the indications as shown by the wide variation in the incidence of choledochotomy in several major clinics ranging from 10 to 45 per cent (Table I). Although it is not possible to define criteria which infallibly lead to the detection of all common duct stones, a reasonable balance must be reached between the added risk of choledochotomy and the potential benefit to the patient. Bartlett and Waddell, in a study of 1,000 cases of choledochotomy, analyzed the relative importance of the various criteria for exploration of the common duct. Except for the actual palpation of stones in the common duct at the time of surgery, the most significant criterion which yielded the greatest percentage of stones was dilation of the duct. When dilation was the only criterion present, 58 per cent of the ducts explored contained stones. This yield was higher than for those cases which were explored on the basis of jaundice or the presence of small stones in the gallbladder. They believe that dilation is the commonest and most accurate indication for choledochotomy. Walters (11) states that he has never seen a common duct of normal size which contained a gall stone. Baker, Diffenbaugh, and others concur in this opinion and have attempted to calibrate all common ducts at operation by placing graduated Bakes dilators alongside the duct. Since the dilated duct is of such importance as a criterion for surgical exploration of this structure, it behooves us to ask "what is the size of the normal common bile duct as seen during an operation"?

SIZE OF NORMAL COMMON DUCT

A thorough review of the literature by Sachs is sufficient to impress on one that there is still a

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TABLE I.—INCIDENCE OF CHOLEDOCHOTOMY AND COMMON DUCT STONES

Author	*Year*	*Total No. of cases*	*Per cent common ducts explored*	*Per cent explored common ducts with stones*	*Per cent total with common duct stones*
Bartlett and Waddell	1958	2243	42.0	38.0	16.0
Baker and Koutsky	1951	478	40.0	50.0	20.0
Glenn	1952	2472	10.5	69.1	7.2
Adams and Stranahan	1947	1104	45.7	36.9	16.8
Walters, Gray, Priestley, and Waugh (12)	1948	1172	23.6	42.6	10.8
Colcock and McManus	1955	1356	36.7	28.5	10.4
Strohl, Diffenbaugh, and Guynn*	1952	25,807	23.0	48.6	11.3

*Collective review.

striking lack of agreement among investigators as to the normal diameter of the common duct. In all probability, each author is correct in his premise, and the difference in the measurement given lies in the methods used. In determining the diameter of the duct, consideration should be given to the type and the site from which measurements are made. Anatomically, the duct is more constant in its middle third and all measurements should be made in this area, or as close to it as possible.

It has been assumed by many that the diameter of the common duct as measured on cadavers can be used as a base to evaluate whether the duct is dilated at surgery. This measurement is inaccurate for clinical use since at autopsy the duct is devoid of: (1) circulating blood and lymph; (2) muscular action; (3) circulating bile flowing under pressure; (4) drug, hormone, and nervous influences. The average size of 0.63 centimeter determined in the cadaver is, therefore, not to be used as a basis for judging the normalcy of the duct in vivo. Handling and fixation of tissue also alter the accuracy of the measurement. In order to obtain a more accurate measurement, Royer and Solari measured the internal diameter of the duct in 100 fresh, unfixed, cadaver specimens, without altering the anatomic relationship of the duodenum, pancreas, and extrahepatic biliary tract. They cannulated the hepatic and Wirsung ducts and injected barium under measured pressure with fluoroscopic control, until it had reached the duodenum. Roentgenograms were taken with the film in close contact with the specimen. The internal diameter of the common duct at its central portion was found to average 0.54 centimeter. This is practically identical with measurements in vivo with intravenous cholografin.

Roentgenographic measurement of the common duct using cholografin is bound to be smaller than the size measured at operation. Only the duct lumen is measured and the additional width of the wall on each side, which may be considerable, is not included. The average roentgenographic size of 0.56 centimeter is only to be compared to other roentgenographic measurements and cannot be used as a base line for evaluating dilation at the operation. Furthermore, in a study of 300 cases correlated with surgical exploration, it has been shown that the size of the duct as measured roentgenographically, is not as significant as the time-density determination in estimating the presence or absence of obstruction. In the case of unobstruction, there is a rapid decrease in the density of dye after 45 minutes, whereas in the obstructed duct, the density of dye after 2 hours is not significantly less than after 1 hour.

In oral cholecystographic studies, the common duct is seen after a fat meal and the contracted gallbladder with its increased pressure, squirts contrast medium in a jetlike stream into the common duct. The entire lumen may not visualize and the diameter may seem very narrow.

The measurement of the common duct which is taken during operative or postoperative T-tube cholangiograms is also not valid for comparison with the size measured at surgery. This method, even under ideal physiologic conditions, is still a retrograde examination, and the common duct may be considerably distended during the examination. In a recent comparative study of 200 patients, who had both cholografin and operative cholangiograms, the mean diameter of the common duct in the operative cholangiograms was 0.7 centimeter and in the

cholografin studies, 0.5 centimeter. After administration of morphine, constriction of the sphincter of Oddi with proximal dilation of the common duct occurred with increase of the intravenous measurement by 0.3 centimeter to approximate the operative cholangiographic measurements. Not one instance of compensatory dilation of the common duct was present after cholecystectomy.

What constitutes a dilated common duct at operation has not been sharply defined. Descriptions such as "about half an inch," "fountain pen," or "thumb" are vague and insufficiently accurate to be the basis for invading so vital a structure. To obtain the true normal diameter of the common duct in vivo would require accurate operative measurement of this structure on patients who required surgery for a pathologic condition unrelated to the biliary tract when the duct was presumably entirely normal. We believed that the dissection with exposure of the common duct which is necessary for such measurement was too hazardous to perform on subjects in whom this procedure was not required. However, since our concern about the size of the duct is manifest primarily during biliary operations, we measured the ducts which were ordinarily exposed as part of the necessary technique of biliary surgery.

CLINICAL MATERIAL

From 1954 to 1956, the ducts in a total of 57 cases were measured. In 46 of these cases, disease was limited only to the gallbladder. In 1 case, no biliary disease existed. The remaining 10 cases demonstrated disease which could account for dilation of the common duct: 6 choledocholithiasis, 2 chronic pancreatitis, 1 carcinoma of the head of the pancreas, and 1 carcinoma of the common bile duct. Further data on these patients are shown in Table II.

METHOD OF MEASUREMENT

A specially designed caliper is employed which has a calibrated side arm giving the measurement either in centimeters or inches. The anatomy of the junction of cystic and common duct is exposed. The overlying peritoneum is incised and peeled away down to the small vessels overlying the ducts. The subperitoneal areolar tissue is cleaned sufficiently along each side of the common duct to allow the caliper blades to fit properly in order to measure the full diameter of the duct. The measurement is taken ¼ to ½ inch below the cystic-common duct junction. This must be performed with care so that the blades of the caliper just touch the duct without compressing its wall. In those instances in which the cystic-common duct junction is more distal than usual, measurement of the common hepatic duct is taken just proximal to where it is joined by the cystic duct.

TABLE II.—CLINICAL MATERIAL (1954–1956) 57 CASES

	No.
Sex	
Female	46
Male	11
Race	
White	26
Non-white	31
Jaundice at time of operation	6
Diagnosis:	
Cholecystitis without cholelithiasis	1
Cholecystitis and cholelithiasis	45
Cholecystitis, cholelithiasis, and choledocholithiasis	6
Chronic pancreatitis	2
Carcinoma of head of pancreas	1
Carcinoma of common bile duct	1
Mistaken diagnosis (granuloma of cecum)	1

Age, 20 to 80 yrs.
Average clinical follow-up, 18 mos. (6 to 28 mos.) in 75 per cent.
Choledochostomy performed, 12 (23 per cent).

RESULTS OF MEASUREMENTS

The cases in this study were divided into 2 groups as follows:

Group 1. In 47 cases, no stones or other pathologic condition was present to dilate the common duct. This includes 45 cases of cholecystitis and cholelithiasis, 1 case of cholecystitis without stones, and 1 case in which no biliary disease (granuloma of the cecum) was present. This group represents as close to a normal measurement of the common duct as is possible without exposing the common duct in patients not requiring surgery in this area. Range of common bile duct diameter was 0.5 to 1.7 centimeters. The average diameter (weighted mean) was 1.2 centimeters.

Group 2. In 10 cases, there was a competent producing cause for dilation of the common duct. Included here are 6 cases of choledocholithiasis, 2 cases of chronic pancreatitis with enlarged head of the pancreas, and 1 each of tumor of the head of the pancreas and the common bile duct. Range of common bile duct diameter was 1.2 to 2.5 centimeters. The average diameter was 1.8 centimeters.

CONCLUSIONS AND DISCUSSION

No stones or other pathologic condition was evident in cases in which the common duct measured less than 1.2 centimeters in diameter. Some ducts measuring up to 1.7 centimeters were found to be free of stones. In 40 of the 57 ducts which measured 1.2 centimeters or larger, a pathologic condition existed in 25 per cent. The ducts exhibiting the greatest dilation were associated with neoplasm.

Six patients had had jaundice but were not jaundiced at the time of surgery. Of these, only 1 showed stones in the common duct. In 6 other patients jaundice was present at the time of surgery, 3 patients had choledocholithiasis, 1 patient had a carcinoma of the pancreas, and 1 had a carcinoma of the common duct. In the sixth patient, several enlarged nodes were present in the triangle of Calot, and the common duct which measured 1.5 centimeters was free of stones. Thus, the presence of jaundice at the time of surgery is a strong indication for exploration of the duct. A history of jaundice without demonstrable jaundice at the time of surgery would appear to be a far less important indication than dilation of the duct to more than 1 centimeter.

Measurement of 45 cystic ducts in cases of cholelithiasis without common duct disease was made. These ducts ranged in size from 0.1 to 1.3 centimeters. More than 75 per cent of these were in the range of 0.3 to 0.6 centimeter, with an average of 0.5 centimeter. It is interesting to note that in the 6 cases of common duct stones, the average measurement of the cystic duct diameter was 1.0 centimeter.

There were 5 cases of impaction of the cystic duct by stone. In 3 of these, there was associated acute cholecystitis and in 1 there was hydrops of the gallbladder. In these cases of "pathologic cholecystectomy" the average common duct diameter measured 1.2 centimeters. The common concept of dilation of the common duct following cholecystectomy is not supported by our measurements in these cases. Sachs believes that compensatory postoperative dilation of the common duct does not occur. In his comparative study of 200 patients in whom operative cholangiograms and postoperative cholografin studies were performed, not one instance of compensatory dilation of the common duct was present.

In 52 cases of inflammatory and calculous disease of the biliary tract, choledochostomy was performed in 12, or 23 per cent. In 6 cases (50 per cent), no stones were found, and the average diameter of the common duct was 1.4 centimeters. In the other 6 cases, stones were found in 5 and a heavy sediment of debris was noted in 1; in this group, the average diameter was 1.7 centimeters.

We realize that the number of cases studied and measured in this series is too small to warrant definite conclusions. However, should a sizeable number of cases, 300 to 400, confirm the rarity of stones in common ducts smaller than 1.2 centimeters at surgery, then a routine measurement of the common duct in all operative cases would be of significant aid to the surgeon. The measurement is easily performed in less than a minute, and it is our hope that many of the larger clinics will join in this study so that more experience can be accumulated. It should be emphasized that the importance of the measurement in deciding whether to perform a choledochostomy is confined to those cases in which there are no other criteria for exploration of the duct. Certain ducts which are narrower than normal because of stricture associated with infection may also contain stones, but these are not commonly encountered.

SUMMARY

Dilation of the common bile duct is a major indication, and often the only one present, for choledochotomy during biliary operations. Common ducts which are explored because of dilation as the only criterion, yield a higher percentage of stones than those ducts explored for other reasons, such as jaundice or large cystic ducts and small stones in the gallbladder. To know how large a duct must be to be considered dilated, it is necessary to know the size of the normal duct as seen in vivo. This has not been accurately determined in the past; autopsy and roentgenographic measurements are not a suitable base line to judge whether a duct seen at surgery is dilated. We have measured a series of common ducts with a caliper in cases in which no pathologic condition was present which might cause dilation. The mean diameter was found to be 1.2 centimeters. No stones were found in ducts smaller than this in 57 cases. This critical diameter, above which there is an increasing presence of stones, may require revision as more measurements are performed and the series becomes larger. The current number of

negative explorations of the common duct in most large series is 50 per cent. Perhaps a simple measurement at operation may serve to bring this figure down to a more reasonable level.

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THE SURGEON'S LIBRARY

Reviews of New Books

A SUCCINCT and carefully organized account of the pathology of tumors of the urinary bladder is given in the small monograph entitled *Atlas of Tumor Pathology; Tumors of the Urinary Bladder*[1]. Clearly, the authors have given much thought to their task and planned their work well. The photomicrographs are well chosen, technically excellent, and illustrate adequately the different kinds of tumors present in the urinary bladder. The photographs of gross specimens are not as informative as the photomicrographs and, in my opinion, the colored illustrations add nothing important to the fascicle.

The authors point out that "the various types of bladder tumors display not only histologic features traceable to true bladder components but may also show morphologic characteristics of embryologically closely related neighbor organs." The authors rightly emphasize that these are best interpreted as activated histogenetic potentials common to the all cloacal-urogenital tissues rather than as misplaced embryonic remnants.

The most debatable feature of the fascicle is the use of the new word "urothelium" to describe the bladder epithelium and the authors' decision to classify all nonglandular epithelial tumors as urothelial tumors. These types include what are more usually called transitional cell papilloma and carcinoma and squamous cell carcinoma. The reasons the authors have given for coining this new word, "urothelial," are very cogent, but I wonder how many of us will be able to break old habits and use the new word. The authors' belief that there are transitional stages of urothelial tumors from papilloma to papillary carcinoma to transitional carcinoma to epidermoid carcinoma is in complete agreement with my personal observations.

All things considered this is a well written and well illustrated account of the pathology of bladder tumors and offers good value for the money. The authors have put us in their debt for writing such a useful little book. But, then if you know Colonel Ash and Dr. Friedman this should not surprise you.

—*William B. Wartman.*

[1]ATLAS OF TUMOR PATHOLOGY. Section VIII—Fascicle 31a, TUMORS OF THE URINARY BLADDER. By Nathan B. Friedman, M.D., and James E. Ash, M.D. Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Division of Medical Sciences of the National Academy of Sciences—Research Council. 82 pages, 86 illustrations. $1.00. Washington, D. C.: Armed Forces Institute of Pathology, 1959.

THE SECOND EDITION of *Angewandte und topographische Anatomie*[2] by Gian Töndury has been revised and enlarged; however, the basic plan of the book remains unchanged. The volume is intended as both a textbook for the medical student and a reference book for the practicing physician, especially the surgeon.

It is divided into three main parts: the trunk (with subdivisions on thorax, abdomen, and back), the head and neck, and the extremities. Much of the book is descriptive anatomy, presented on a regional basis. Side by side with this is found practical clinical material as it relates to the anatomy. Since the author is convinced that a real understanding of the complicated architecture of the human body can be reached only through knowledge of the embryologic picture, he has included short embryologic sketches—scattered appropriately throughout the volume. This leads also to discussions of variations and anomalies of practical importance.

Obviously, the illustrations should be a prime feature in this type of work. In this case they are excellent and mostly original. There are many full size plates with brilliant color overlay, which adds appeal as well as clarity; smaller, simple schematic black and white drawings; and reproductions of roentgenograms.

The German text is quite manageable. Most of the terminology employed in the labels of the illustrations is that of the *Nomina Anatomica*.

This handsome volume is recommended to all those who seek constantly to increase their knowledge of the structure of the human body.—*Carolyn E. Thomas.*

THE *Encyclopédie médico-chirurgicale* is a series of books in French presenting the subjects of medicine, surgery, and their specialties according to the current state of knowledge. The volume *Anesthésie-réanimation*[3] reviews the specialty of anesthesia. It is published under the combined editorship of Prof. J. Baumann of the Faculty of Medicine of Paris and Drs. E. Kern and J. Lassner. Many authors have taken part in the writing of the different chapters.

The treatise is divided into three sections: general and local anesthesia and resuscitation.

[2]ANGEWANDTE UND TOPOGRAPHISCHE ANATOMIE; EIN LEHRBUCH FUER STUDIERENDE UND ÄRZTE. By Professor Dr. G. Töndury. 2nd ed. 578 pages, 411 illustrations. $18.80. Stuttgart: Georg Thieme, 1959.

[3]ENCYCLOPÉDIE MÉDICO-CHIRURGICALE; ANESTHÉSIE-RÉANIMATION. Edited by J. Baumann, E. Kern, and J. Lassner. Illustrated. Paris: Editions Techniques S. A. Encyclopédie Médico-Chirurgicale, 1958.

A brief review of the history of anesthesia and short chapters on physics and on general physiology as related to anesthesia serve as an introduction to the subject of general anesthesia. Methods of administration, techniques, and complications of general anesthesia are reviewed. The pharmacology of anesthetic and analgesic drugs and of the muscle relaxants, the physical principles upon which anesthetic apparatuses function, and the use of monitoring devices for the measurement of various physiologic variables are described and discussed. Short chapters cover the subject of induced hypotension, artificial hibernation, and induced hypothermia.

The pharmacology of local anesthetic drugs and the methods and techniques of regional, spinal, and epidural anesthesia are reviewed. Chapters on anesthesia as applied to general surgery and the different surgical specialties are presented.

The section related to resuscitation covers questions concerned with theories of coagulation of the blood, with blood groupings and blood transfusions, with plasma-volume expanders, and with electrolytes and fluid balance. Treatment of shock and burns is reviewed. In the chapters on the artificial kidney and on oxygenotherapy the basic principles and their indications are described.

This is a very comprehensive treatise on anesthesia. It fulfills very well its purpose, namely to present in the French language a reference book for instruction and guidance in the principles and methods of anesthesia, which are found and described, for the major part, in the English and American literature.

As is sometimes true of treatises written by multiple authors, many aspects of the subject overlap and a certain amount of repetition is unavoidable. Also, controversy in some statements by different authors does occur, but it remains the privilege of the reader to weigh the advantages and disadvantages of certain methods, having in mind what should be best for the patient. A rather conservative attitude and approach to the controversial subject of artificial hibernation, which originated in France, have been maintained in this book. —*Robert A. Devloo.*

THE APPEARANCE of another book dealing with the treatment of common fractures entitled *Fracture Surgery*[4] must make one examine its object and contents with care to determine if it presents the subject in a clearer, more attractive, or better illustrated form. Especially is this so if the authors' avowed objective is to reach the student, the resident, or those doctors who only occasionally are called upon to treat fractures.

The authors state in the introduction that the book has been written to bridge the gap between the small handbook of fracture treatment and the encyclopedic volume suitable only for the specialist and that it is intended as a ready reference work of a largely pictorial nature.

When a volume is so dedicated, it must strictly live up to its intentions. Methods advocated must be those proved by experience; common problems must be adequately considered and the unusual or bizarre relegated to their rightful place in the background. Illustrations should be lavish and uniformly excellent.

The opening chapters deal with the general care of the injured patient, the treatment of shock, emergency splintage, and the problems of transfusion, all of which are adequately covered.

Displacement of fracture is described in terms of their axial malalignments. These new terms, in no respect, differ basically from the more familiar and accepted descriptive terms of bony deformity, but merely cloak them in a new and unfamiliar guise, and thus serve to confuse rather than simplify.

The section on epiphysial injuries deals largely with complications and by overstressing disturbances of growth gives an erroneous impression of their frequency. In describing apparatus for the reduction of fractures of the lower limbs, the well-leg tractor is included. Even in expert hands, this equipment gives rise to so much trouble that most orthopedic surgeons have ceased to use it.

Compression fractures of the lumbar spine are reduced and immobilized in a hyperextension plaster jacket, though mention is made of the current British practice of early mobilization, using simple brace fixation.

One would agree that an exact reduction is desirable in supracondylar fractures of the humerus in children, but this may lead in some instances to more damage by unwise attempts at remanipulation, for in most instances remodeling occurs with growth, and so long as medial or lateral tilting is avoided, rarely is there any final deformity or limitation of movement. It is for this reason that one should comment on the curious statement that excessive callus formation after this injury may cause limitation of flexion or extension. This is surely most unusual. This section also contains a detailed discussion of the various types of condylar fracture and their treatment, and is clearly out of place in this volume. Figure 209 shows the wedge of bone to be removed from the lateral rather than the medial side of the humerus to correct the valgus deformity illustrated.

In dealing with fractures of the ulnar shaft, plating is the procedure of choice for internal fixation. Intramedullary pinning is so suitable for this bone that one would like to have seen its use included. In the illustrations of injuries of the lower radial epiphysis, undue attention has been directed to growth disturbances. After this injury, and considering the gross displacement often present, such a complication is surprisingly rare.

Fractures of the fingers and metacarpals are sometimes treated by pulp traction, with the finger in full extension. This is not regarded by most hand surgeons as good practice. A similar observation could be made on the use of the Thomas type of finger splint.

The Jahss method of pelvic compression for separation of the symphysis pubis, using long leg plasters and turnbuckles, does not recommend itself as one free of complications in inexpert hands. Other simpler methods would be preferable.

In discussing the treatment of slipping of the upper femoral epiphysis, the authors use cast or brace fixa-

[4]FRACTURE SURGERY; A TEXTBOOK OF COMMON FRACTURES. By Henry Milch, M. D., and Robert Austin Milch, M.D. With a chapter on anesthesia by Herbert D. Dubovsky, M.D. 470 pages, 671 illustrations. $17.50. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1959.

tion in some early cases. Most surgeons have found both of these unreliable in preventing further slipping, and prefer the security of internal fixation. Conversely, they have not found such fixation necessary in impacted abduction fractures of the femoral neck. The Milch resection angulation operation is the standard procedure in dealing with subcapital fractures which develop complications of union or avascular necrosis. One must question the statement that operative fixation is necessary for separated fractures of the greater trochanter.

In fractures of the femoral shaft, medullary nailing is stated to be the method of choice in multiple or severely comminuted fractures of the mid portion. Surely, this method finds its best use in the transverse or short oblique fracture, where it can be relied upon to give secure fixation.

Closed spiral fractures of the tibia are treated by Kirschner wire transfixation. Segmental fractures are treated by the Lottes nail or by fixation with a very long plate and multiple screws. This latter method is not in general favor, owing to the wide exposure necessary and the subsequent risk of nonunion. The tibiofibular synosteosis operation is advocated as the standard procedure for nonunion; simpler and more usual methods of bone grafting receive little or no attention.

This book sets out with a high target and falls short in its aim. Many sections are excellent, but some of the methods of treatment advocated, although they may be successful in the hands of the authors, have not found general acceptance. In some chapters, too much stress is laid on the unusual to the detriment of the commonplace. Some of the illustrations and roentgenographic reproductions lack clarity. It is for these reasons that the book cannot be recommended without reserve to the group of doctors for whom it was intended. —*Harold Bolton.*

THE ATTRACTIVE VOLUME *A téchnica das ressecções pulmonares*[5] by Edidio Guertzenstein deals with the technique of pulmonary resections. It is composed of 18 chapters and presents 220 original illustrations most of which show the techniques employed by the author in about 400 operations. After reviewing historical data on pulmonary resection from the time it was first performed by Tuffier in 1891, the author analyzes in the 7 following chapters various problems concerning preoperative care, cardiac arrest, thoracotomy, pulmonary isolation and liberation, technique of treatment of blood vessels, and the technique of closure of the bronchi. For the latter, he uses a modification of the Chamberlain method.

Two chapters are devoted to surgical anatomy. They are well illustrated and form the basis for an easier understanding of the section devoted to the indications for and techniques of pneumectomy, lobectomy, segmental resection, and simultaneous bilateral and partial resection. These chapters are profusely illustrated, almost to the point of forming an atlas and showing the technical details step by step.

In the last 4 chapters, the author discusses in considerable detail thoracic drainage, postoperative care, supplementary thoracoplasty, and complication.

In the foreword, the author states that it was his intention to prepare a book that would describe the technique of pulmonary resection in a practical and accessible form. He has accomplished his purpose admirably, and this up-to-date book will appeal to all Portuguese-speaking people interested in thoracic surgery. —*E. Damiao Pires.*

THE SINGLE VOLUME *Textbook of Surgery*[6] continues to be outstanding in its third edition for use by the medical student, principally, the surgical intern, the resident, and those responsible for their teaching. It represents the efforts of 40 contributors, most of whom practice in the same hospital and teach in the same medical school. Their presentations are simple, straightforward, and informative as are many of the line drawings, photographs, and roentgenograms, supplemented by the colored plates of the Ciba collection. The physical make-up of the book is of the highest quality. It is easily readable with convenient placement of illustrative art work.

The chapters on pediatric surgery, fractures, cardiovascular surgery, and many others are outstanding. In very few instances has the brevity of the presentation detracted from the present day information which such a text should contain. A test of this text's use as a guide in the teaching of medical students has been carried out in conjunction with the standard American texts. It compares very favorably with the single volume American books in current usage in our medical schools. —*John M. Dorsey.*

THE RESULTS of clinical and experimental research which pertain to diagnosis and treatment of peripheral vascular disease are presented in the volume by Dr. Glasser entitled *Principles of Peripheral Vascular Surgery.*[7] The author has not wished to present in detail surgical techniques or to cover in any degree the preoperative and postoperative management of patients undergoing surgical treatment of vascular lesions. The result is, therefore, a valuable text which contributes principally to organization of material and aids in the recognition and understanding of vascular pathology and, to a much lesser degree, to the surgical treatment of the lesions described.

Diseases of the vascular system are given broad coverage. The chapters on venous thrombosis, varicose veins, and stasis disease are particularly well handled. The information presented concerning neurovascular syndromes of the upper extremity is excellent.

Throughout the book the author avoids being dogmatic in the discussion of unsettled points, and frequently refers to authorities for many statements. Each chapter carries a liberal number of references which are clearly identified so as to aid one who wishes to find further details and information.

[5] A TÉCHNICA DAS RESSECÇÕES PULMONARES; UM ESTUDO DA ANATOMIA CIRÚRGICA E TÉCNICA OPERATÓRIA DE ACORDO COM A CONDUTA MAIS ATUALISADA. By Edidio Guertzenstein. 324 pages, illustrated. Rio de Janeiro: Livraria Atheneu S. A., 1958.

[6] TEXTBOOK OF SURGERY. Edited by H. Fred Moseley, M.A., D.M., M.Ch.(Oxon), F.A.C.S., F.R.C.S.(Eng.), F.R.C.S.(C). 3rd ed. 1336 pages, 738 illustrations and 108 color plates. $17.00. St. Louis: The C. V. Mosby Co., 1959.

[7] PRINCIPLES OF PERIPHERAL VASCULAR SURGERY. By S. Thomas Glasser, M.D., C.M., F.A.C.S., F.A.C.A. 410 pages, illustrated. Philadelphia: F. A. Davis Co., 1959.

There is some incompleteness in the handling of vascular trauma and in material on surgical reconstruction in the treatment of chronic occlusive arterial disease.

The text is well written. Highly specialized portions are made understandable by their graded presentation. The fact that actual surgical problems are lightly treated is adequately and perhaps properly compensated for by references to current or recent literature. The text should be useful in the introduction of medical students to the field of vascular disease and the possibilities of surgical therapy.

—*Armand C. Julian.*

THE FIFTH VOLUME of *Cancer*[8] is limited, though extensive in scope, to radiotherapy. Again, the contributors are mostly from England, with emphasis on London. All are respected as very competent specialists.

The first 8 chapters are devoted to the principles of radiation, including the physical and the biologic properties as well as dosage and methods. There is a separate chapter on radioisotopes and two on radiation protection, as well as radiation reaction and treatment. All remaining chapters are devoted to the specific organs and tissues. As would be expected, there is a certain flexibility in composition but a fairly uniform method of presentation. The various authors did not hesitate to express opinions.

One trend in particular impressed this reviewer and that is that no one author represented radiation therapy as a "cure all." There was definite emphasis on a relation to surgery and on the need for positive biopsy prior to instituting treatment.

There are many diagrams demonstrating the recommended or preferred methods of usage of the various forms of radiation. Low voltage, high voltage, radium, and radioisotopes are discussed individually. Tables are utilized to indicate radiocurability, radiosensitivity, and radioresponsiveness. Much of this material may be of interest only to the therapist rather than to the oncologist as such. However, all of it is of value especially in a reference volume.

Somehow the subject on cancer of the reticuloendothelial system seems to be presented with a certain hesitancy as to the value of radiation. Thus far, chemotherapy has not replaced it.

There are a few phrases which may be questioned. On page 339, the statement is made that "sarcomas of bone are relatively rare . . . they represent roughly thirty per cent of all primary malignant tumours." This must be 3 per cent. Also on page 250, "the cervix uteri is a more common primary site than the corpus uteri." This is not true now in the United States as these are almost equal in frequency. On page 160: "metastases to the jaw are common in advanced cases of carcinoma of the breast." This has not been a common finding in the United States.

Those sections dealing with the uterus, the breast, the head and neck, the bone, and the skin are especially well covered. In summary, the volume maintains the standards of its four predecessors.

—*M. C. Wheelock.*

[8]CANCER. Edited by Ronald W. Raven, O.B.E.(Mil.), T.D., F.R.C.S. Vol. V. Part IX. RADIOTHERAPY. 425 pages, 136 illustrations. $18.00. London: Butterworth & Co., Ltd., 1959.

IN THE EDITOR'S WORDS, the *Textbook of Oral Surgery*[9] "is designed to fit the needs of the undergraduate senior student." Presentation is made in an orderly, readable manner by faculty members of dental schools "in the sequence in which it is given to the senior dental students in the lecture courses."

The first chapters are devoted to the general fundamentals of surgery: surgical technique, infections, hemorrhage, and shock, described in some detail and amply illustrated. Diagnosis and treatment of conditions peculiar to the mouth because of the teeth, including abnormalities, periapical infections, cysts, osteomyelitis of the jaw, and diseases of the maxillary sinus, are well presented. The chapters on the temporomandibular joint and developmental deformities of the jaws are equally worthy. A discussion of facial injuries, which includes the repair of soft tissue involvement and burns, congenital deformities as cleft lip, tumors of the salivary glands, and carcinoma of the mouth, is evidently included only for completeness and to acquaint the student with the existence of these conditions.

—*Minot P. Fryer.*

WHILE THE SECOND EDITION of *Diseases of the Nose, Throat, and Ear*[10] by Jackson and Jackson retains the original pattern of presentation, it has been completely rewritten and augmented by numerous, entirely new chapters. The Editors and 61 outstanding authorities have brought the text up to date by deleting obsolete material and including the new techniques and new knowledge developed during the unprecedented advances in otorhinolaryngology since the publication of the first edition.

Part 1, dealing with the nose and accessory sinuses, contains well indexed and reliable information on the common diseases and important abnormalities of the external nose, nasal chambers, and septum. The systematic, comprehensive, and authoritative chapters on the paranasal sinuses include a competent review of the current acceptable application of chemotherapy and the modification of surgical procedures resulting from the effectiveness of the new drugs. Other additions include meritorious sections on tumors of the nose and sinuses and traumatic maxillary surgery, and a concise, exhaustive chapter on corrective plastic surgery of the nose, profusely illustrated with meticulous line drawings and instructive photographic reproductions.

The mouth and fauces are considered in Part 2, which in addition to the standard subjects, contains extensive information on diseases of the mouth and tongue, diseases of the salivary glands, and blood dyscrasia. Part 3, is limited to the ear, and has been expanded by the inclusion of chapters on psychogenic deafness, chronic infections of the middle ear, and mobilization of the stapes for otosclerotic deafness. A many-sided review of current knowledge in the

[9]TEXTBOOK OF ORAL SURGERY. Edited by Gustav O. Kruger, B.S., A.M., D.D.S., F.A.C.D. Drawings by Biagio J. Melloni, 573 pages, 489 illustrations. $12.75. St. Louis: The C. V. Mosby Co., 1959.

[10]DISEASES OF THE NOSE, THROAT, AND EAR. Edited by Chevalier Jackson, M.D., Sc.D., LL.D., L.H.D., F.A.C.S., and Chevalier L. Jackson, M.D., M.Sc., F.A.C.S. 2nd ed. 886 pages, 1,193 illustrations including 16 plates in color. $20.00. Philadelphia and London: W. B. Saunders Co., 1959.

field of otology is afforded by the introduction of such topics as the functional alterations from sensory-neural lesions and a discussion of the subject of aviation otology.

Part 4, devoted to the larynx and hypopharynx, and Part 5, dealing with the bronchi and esophagus, are the contributions of recognized world authorities and may well prove to be the definitive text in laryngology and bronchoesophagology. The coverage is encyclopedic and includes full consideration of congenital abnormalities and functional disorders. An important contribution consists of the fine description of the Brien King operation for bilateral laryngeal paralysis. Especially impressive are the detailed and readily understood descriptions of the generally accepted techniques involved in diagnosis and treatment. Previously, much of this information could be obtained only after a time-consuming search through many reference sources.

Throughout the volume, the diseases are discussed in a total medical context—etiology, pathology, course and termination, symptoms, complications, sequelae, chemotherapy, and surgical treatment. Exceptionally complete descriptions are given of diagnostic and surgical techniques and the clinical manifestations are carefully portrayed.

The book is noteworthy for the number and quality of the illustrations; it contains 1,193 illustrations of which 16 plates are in color. A practical bibliography is appended to each topic. This new edition will prove invaluable to otolaryngologists and bronchoesophagologists and serve as a sound reference work for those physicians and surgeons whose interests are related to the specialty. —*Harry P. Schenck.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgement must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

Principles and Practice of Obstetric Anaesthesia. By J. Selwyn Crawford, M.B., Ch.B. 128 pages, illustrated. $4.00. Springfield, Ill.: Charles C Thomas, 1959.

Color Atlas and Management of Vascular Disease. By William T. Foley, M.D., F.A.C.P., and Irving S. Wright, M.D., F.A.C.P. 170 pages, illustrated. $18.00. New York: Appleton-Century-Crofts, Inc., 1959.

Das diagnostische Pneumoperitoneum. By Prof. Dr. Med. A. Gebauer. Preface by Prof. Dr. F. Hoff. 69 pages, 78 illustrations. $4.30. Stuttgart: Georg Thieme, 1959.

Diseases of Medical Progress. By Robert H. Moser, B.S., M.D. Foreword by F. Dennette Adams, M.D. 131 pages. $4.75. Springfield, Ill.: Charles C Thomas, 1959.

Resuscitation of the Unconscious Victim; a Manual for Rescue Breathing. By Peter Safar, M.D., and Martin C. McMahon. Illustrations by Colin E. Thompson, Jr. 79 pages, illustrated. $1.75. Springfield, Ill.: Charles C Thomas, 1959.

Die Wirbelsaeulenleiden und ihre Differentialdiagnose. By Prof. Dr. J. E. W. Brocher. 457 pages, 287 illustrations. DM 128.—Stuttgart: Georg Thieme, 1959.

Combined Textbook of Obstetrics and Gynaecology; for Students and Practitioners. Edited by Dugald Baird, B.Sc., M.D., D.P.H., F.R.C.O.G. 6th ed. 936 pages, 492 illustrations, 27 in color. $15.00. Edinburgh and London: E. & S. Livingstone Ltd., 1957; Baltimore: The Williams & Wilkins Co., exclusive U. S. Agents.

Open Reduction of Common Fractures. By Oscar P. Hampton, Jr., M.D., F.A.C.S., and William T. Fitts, Jr., M.D., F.A.C.S. 212 pages, 72 illustrations. $8.75. New York and London: Grune & Stratton, 1959.

A Synopsis of Anaesthesia. By J. Alfred Lee, M.R.C.S., L.R.C.P. 4th ed. 616 pages, 72 illustrations. $6.50. Baltimore: The Williams & Wilkins Co., 1959.

The Surgeon and the Child. By Willis J. Potts, M.D. 255 pages, illustrated. $7.50. Philadelphia and London: W. B. Saunders Co., 1959.

Orthopaedic Surgery. By Sir Walter Mercer, M.B., Ch.B., F.R.C.S.(Hon.). 5th ed. 1075 pages, 422 illustrations. $12.00 Baltimore: The Williams & Wilkins Co., 1959.

A Synopsis of Obstetrics and Gynaecology. By Aleck W. Bourne, M.A., M.B., F.R.C.S.(Eng.). 12th fully rev. ed. 632 pages, 151 illustrations. $8.00. Bristol: John Wright & Sons Ltd., 1959; Baltimore: The Williams & Wilkins Co., exclusive U. S. Agents.

The Life and Times of Sir Charles Hastings; Founder of the British Medical Association. By William H. McMinemey, M.A., D.M., F.R.C.P., D.P.M. 516 pages, illustrated. Edinburgh and London: E. & S. Livingstone Ltd., 1959; Baltimore: The Williams & Wilkins Co., exclusive U. S. Agents.

The Physiology and Treatment of Peptic Ulcer. Edited by J. Garrott Allen. 236 pages, illustrated. $7.50. Chicago: The University of Chicago Press, 1959.

Symposium on Pulmonary Ventilation. Edited by Dr. R. P. Harbord and Professor R. Woolmer. Held in Leeds under the auspices of *The British Journal of Anaesthesia*. Altrincham: John Sherratt & Son, 1959; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

Roentgens, Rads, and Riddles. A Symposium on Supervoltage Radiation Therapy. Edited by Milton Friedman, M.D., Marshall Brucer, M.D., and Elizabeth Anderson, U. S. Atomic Energy Commission. 495 pages, illustrated. $3.50 (paper bound). Washington: U. S. Government Printing Office, 1959.

Klinik und Praxis der Urologie; Klinik, Indikation, Diagnostik Operative und Instrumentelle Eingriffe Nachbehandlung. By Prof. Dr. Werner Staehler. Vol. I. 892 pages, 1034 illustrations. $57.15. Stuttgart: Georg Thieme, 1959.

Experimental Surgery; Including Surgical Physiology. By J. Markowitz, M.B.E., M.B.(Tor.), J. Archibald, D.V.M., M.V.Sc., and H. G. Downie, D.V.M. 4th ed. 931 pages, 580 illustrations. $12.50. Baltimore: The Williams & Wilkins Co., 1959.

Medical Management of the Menopause. By Minnie B. Goldberg, M.D. 98 pages, illustrated. $4.50. New York and London: Grune & Stratton, Inc., 1959.

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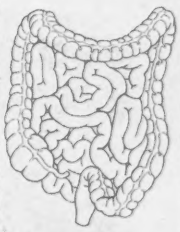

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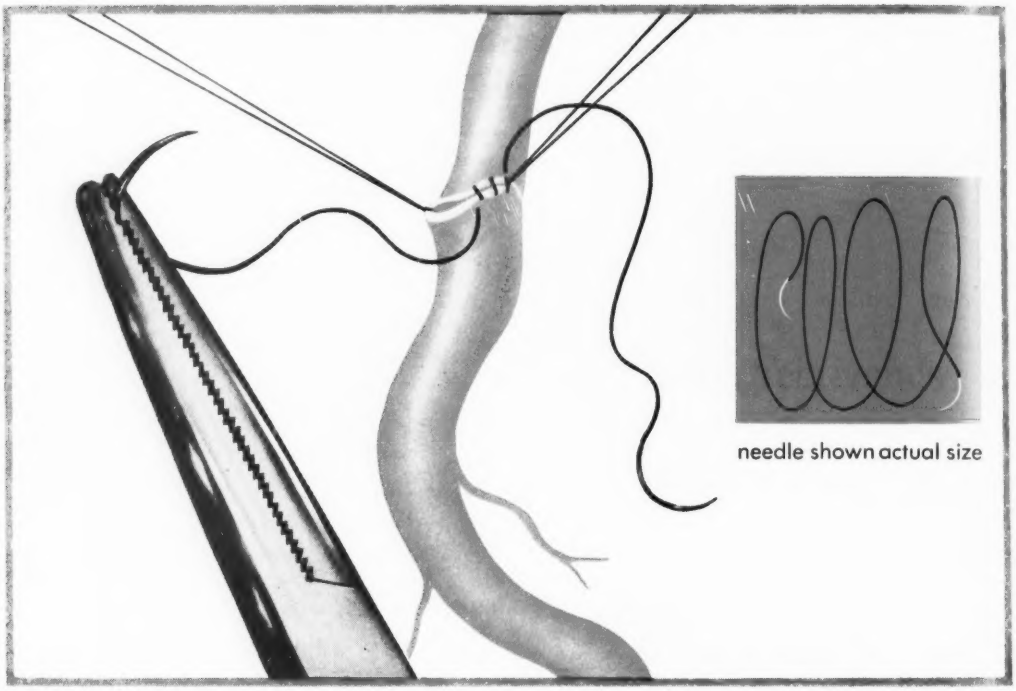

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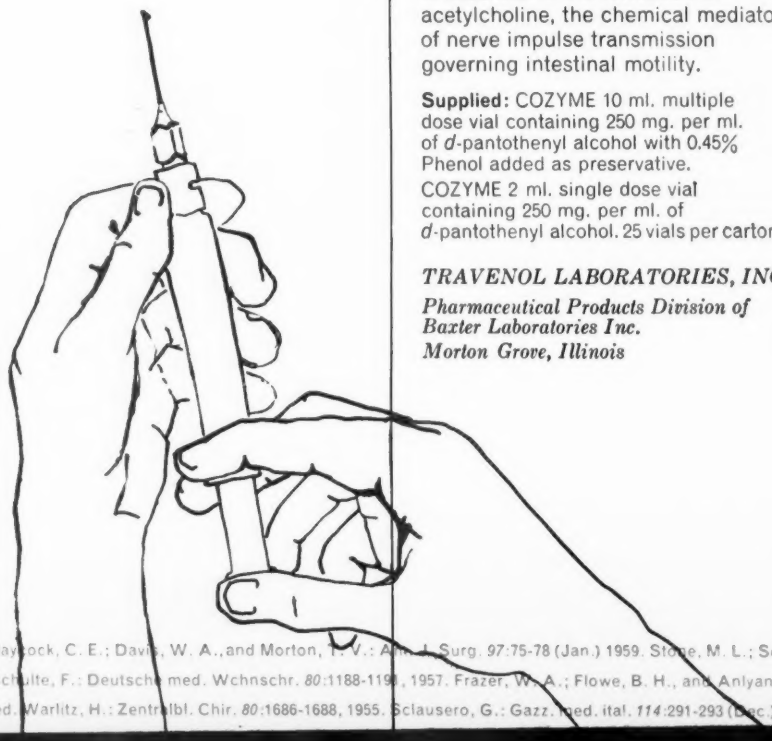

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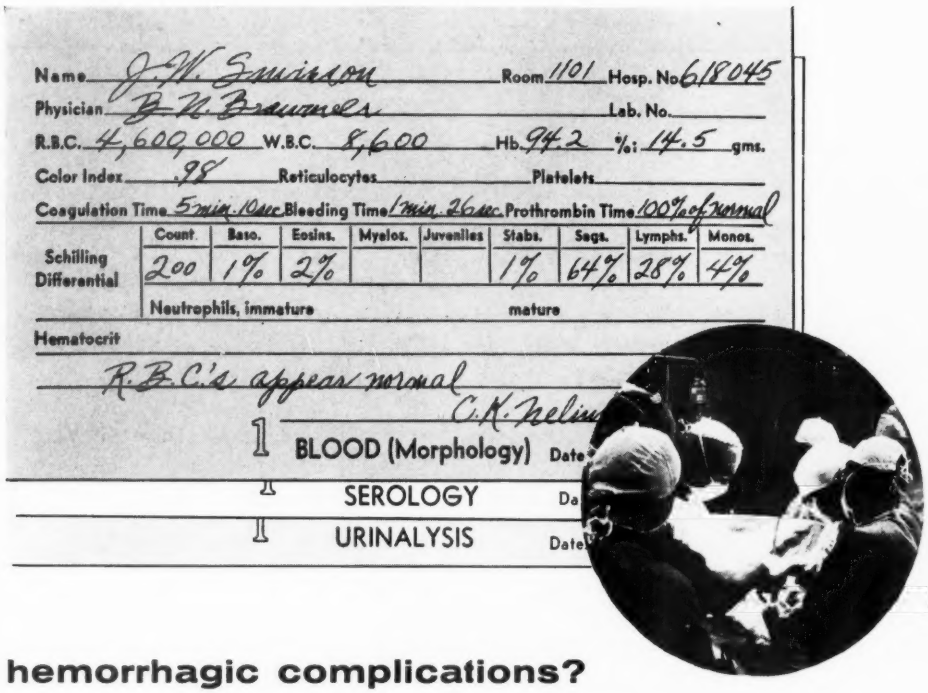
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over a cup of coffee...

INTERN: I've been wondering why you prescribed AZOTREX for the cystitis case. Are all three agents – tetracycline, sulfa and azo dye – really necessary?

ATTENDING MAN: Well, whenever I treat a urinary infection, I have three things in mind. First, I want to relieve pain, frequency and urgency as soon as I possibly can. Next, I want to eliminate the bacteria in the urine and easily accessible pathogens in the mucosa. Finally, I'd like to clear up the deeper foci of infection and thus help prevent recurrence. With AZOTREX, I have a good chance of accomplishing all three.

INTERN: I can go along with AZOTREX as far as relief of symptoms is concerned. The azo dye is a good urinary analgesic, so I agree with you on the relief of pain. Also I know that some patients get reassurance from the change in color of the urine.

But, why treat the infection with both tetracycline and sulfamethizole? Combination antibacterial therapy has come under some editorial fire recently. You know—no synergistic or additive effect in most cases. Generally, we're supposed to use the single antibiotic or sulfa which the "bugs" are most sensitive to.

ATTENDING MAN: I agree wholeheartedly. That's why I sent a specimen to the lab for culture and sensitivity. But right now we don't know the organisms involved, and it's going to be 2 or 3 days before we get the lab report.

When I have to work in the dark, I want as broad antibacterial coverage as possible. Moreover, if this is a mixed infection – and these are fairly common – our chances are likely to be better with a combination like AZOTREX. Tetracycline and sulfamethizole are effective against many strains of staph, strep, proteus and pneumococci. Rhoads recommends this type of combination therapy for Pseudomonas, *A. aerogenes*, *B. faecalis* and *E. coli*.

So I figure AZOTREX is a good way to start. Should the sensitivity tests indicate that another antibacterial agent is preferable, we'll switch to that.

INTERN: You also said something about deeper foci of infection in the kidney . . . ?

ATTENDING MAN: We are both aware that a foreign body or obstruction will cause persistence of the infection and should be attacked directly. However, infection may persist or recur even in their absence.

Kass has suggested that this may be due to inadequate drug levels in tissues with a poor blood supply. Such circumstances may account for the reappearance, even after apparent sterilization of the urine, of the original organism with the same antibiotic sensitivity. Also, inadequate local tissue concentrations might fail to kill all bacteria and encourage the emergence of resistant strains. In Kass' view, high blood levels of drug are necessary to permit penetration of sufficient amounts to be of therapeutic value.

Tetracycline—especially in its phosphate form—is rapidly absorbed from the G. I. tract and produces high blood and tissue levels. According to Mason, sulfamethizole is one of the most soluble sulfonamides; this means high urinary antibacterial concentrations without crystalluria. I'd suggest you look this up in the U. S. Dispensatory and in N. N. D.

INTERN: O. K., I'll look it up. In the meantime I'll try to keep an open mind.

ATTENDING MAN: So far, we've talked only about "bugs and drugs". Let's not forget we're dealing with a sick person who will have to take medicine for a long time. It's a lot easier and more convenient to take one capsule instead of three. Now, how about another cup of coffee?

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References: Rhoads, P. S.: Postgrad. Med. **21**:563 (June) 1957; Kass, E. H.: Am. J. Med. **18**:764 (May) 1955; Mason, J. T. in Conn., H. F.: Current Therapy—1959, W. B. Saunders, Philadelphia, p. 342; Osol, A. and Farrar, G. E., Jr., Eds.: The Dispensatory of the United States of America 25th edition, Philadelphia, J. B. Lippincott Co., 1955, p. 1881; New and Nonofficial Drugs 1959, Philadelphia, J. B. Lippincott Co., p. 60.

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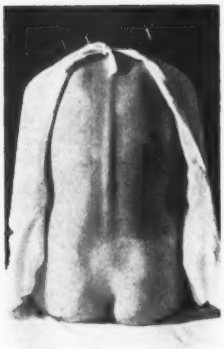

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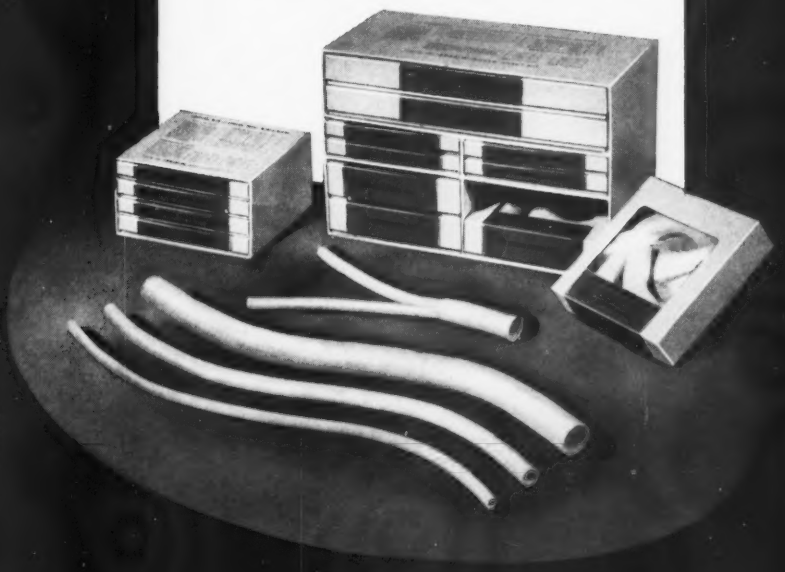

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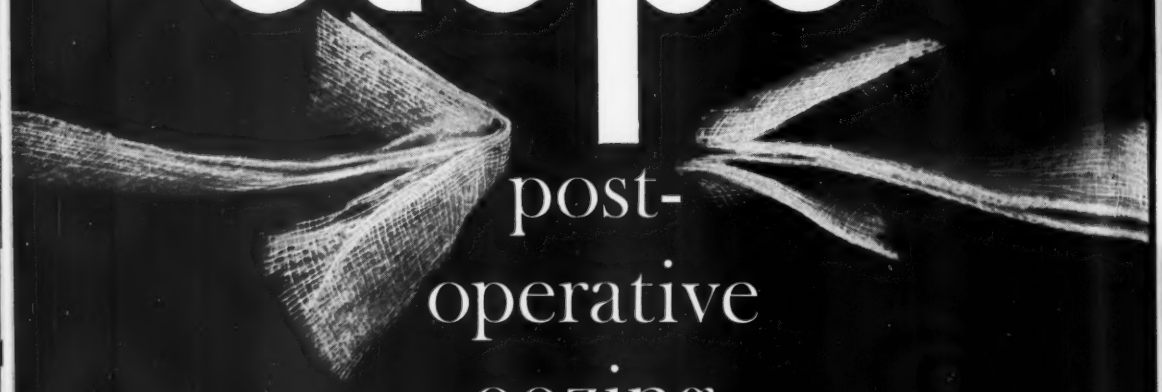

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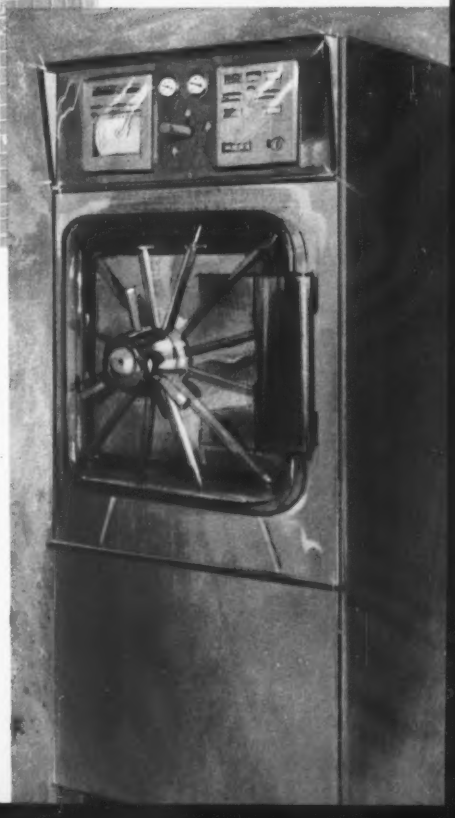

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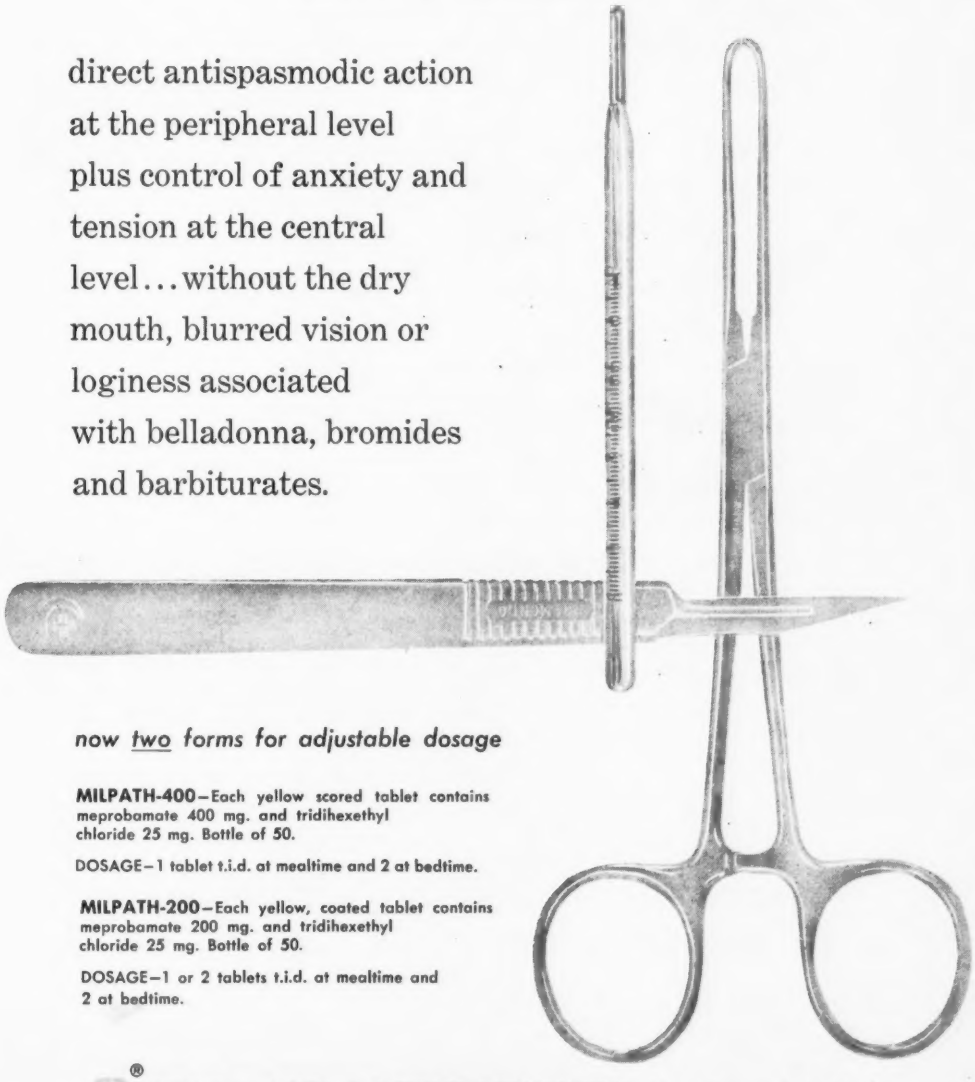

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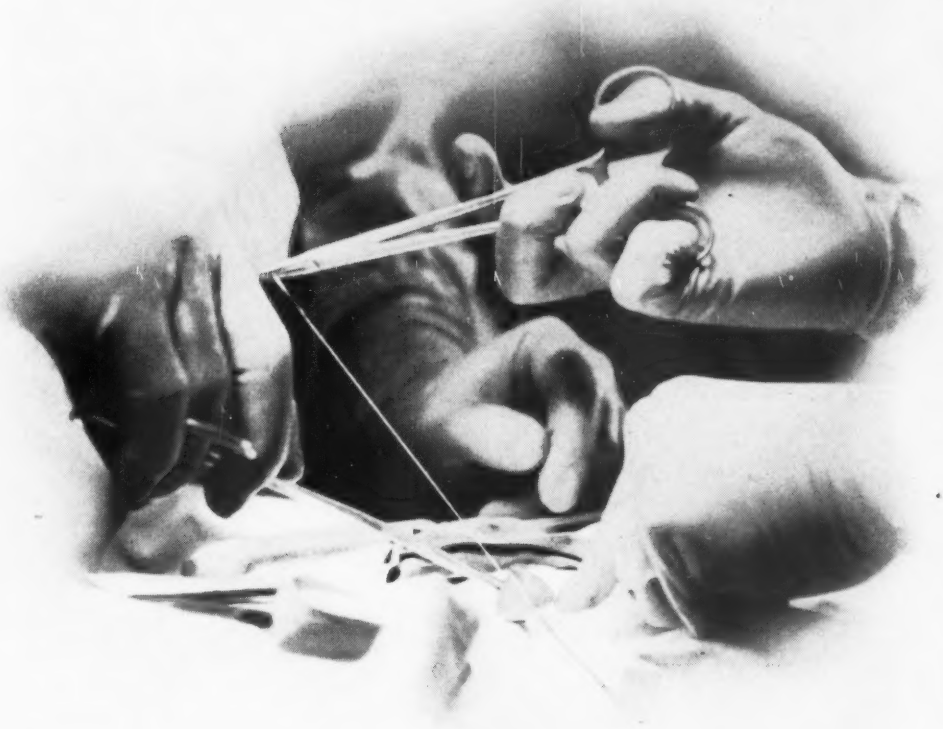

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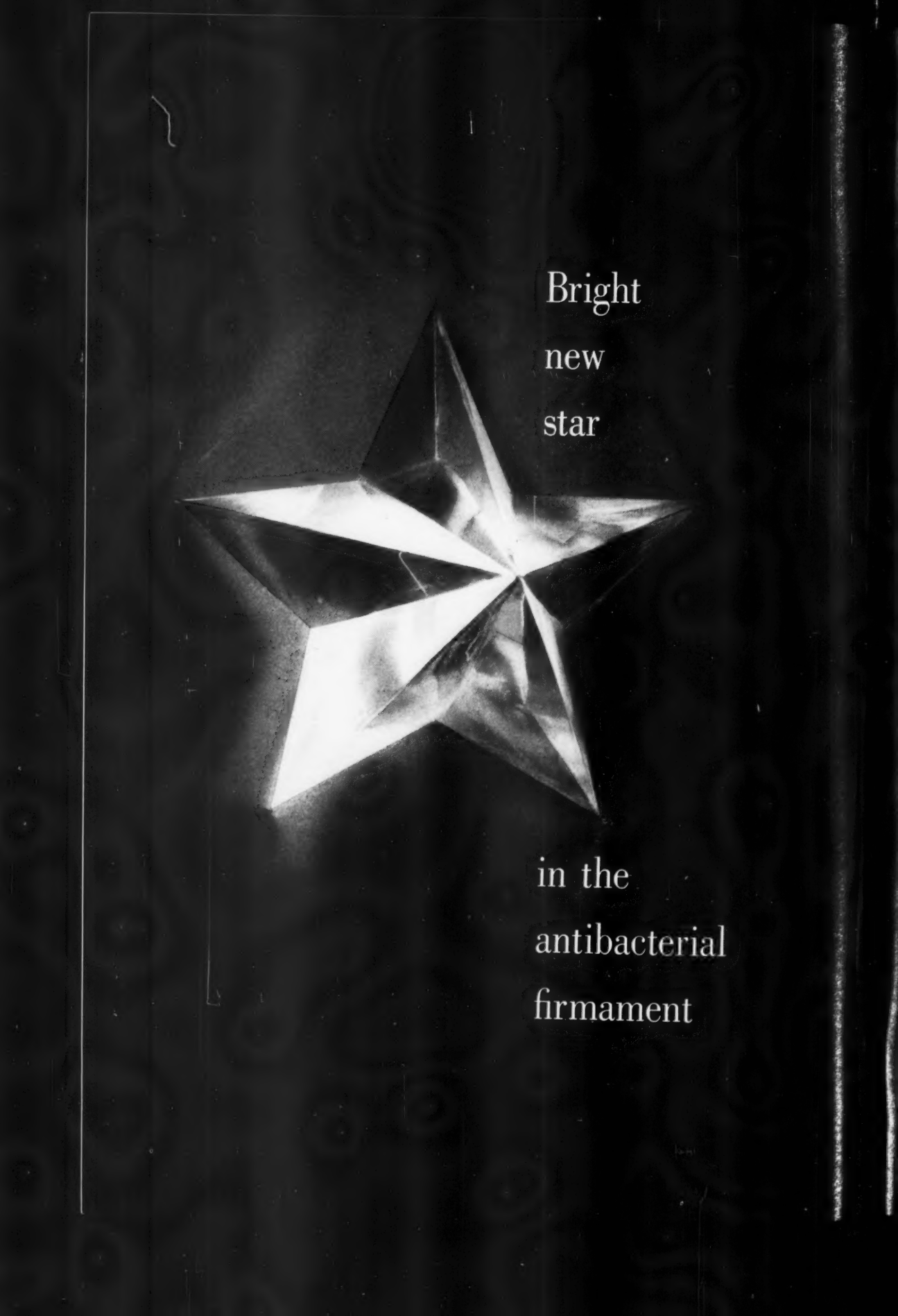
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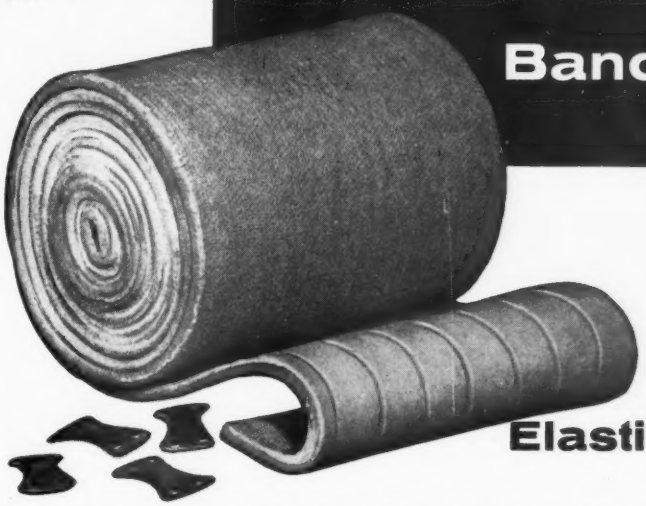

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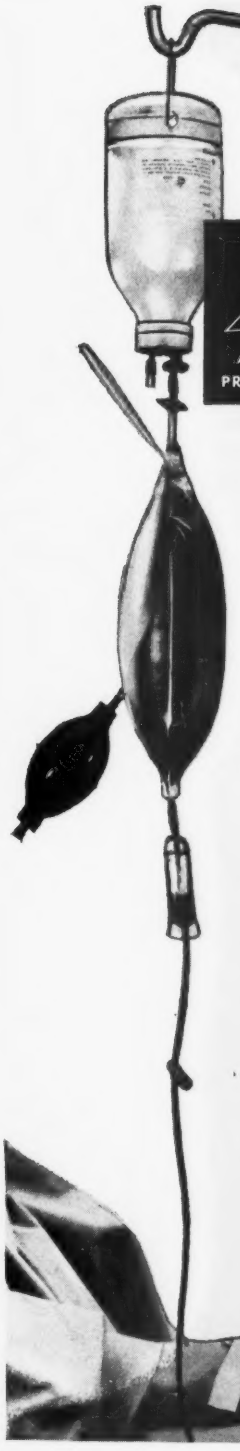

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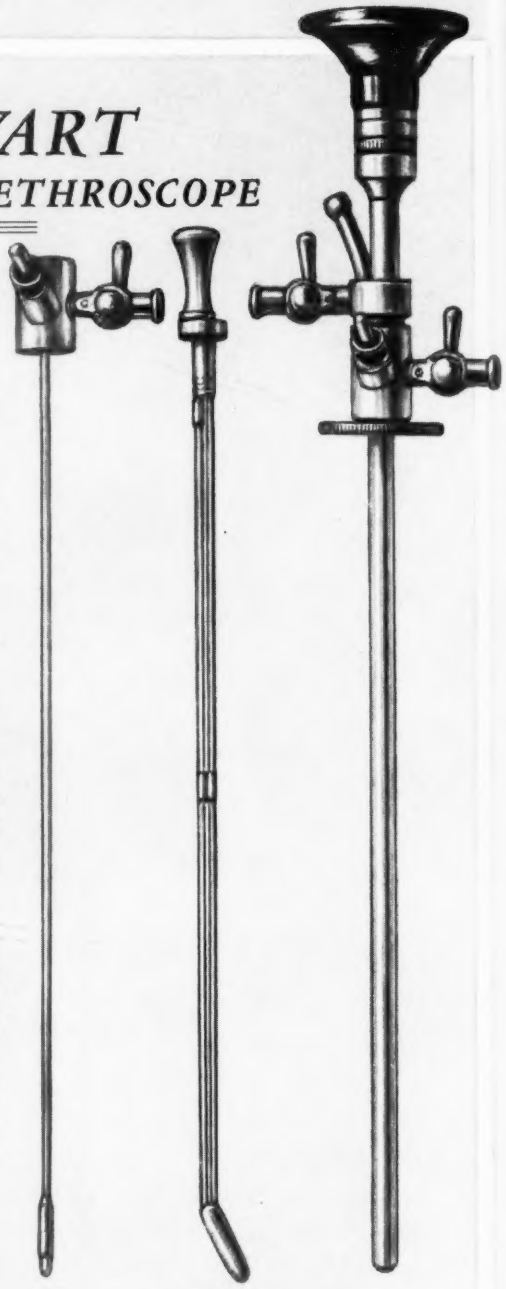

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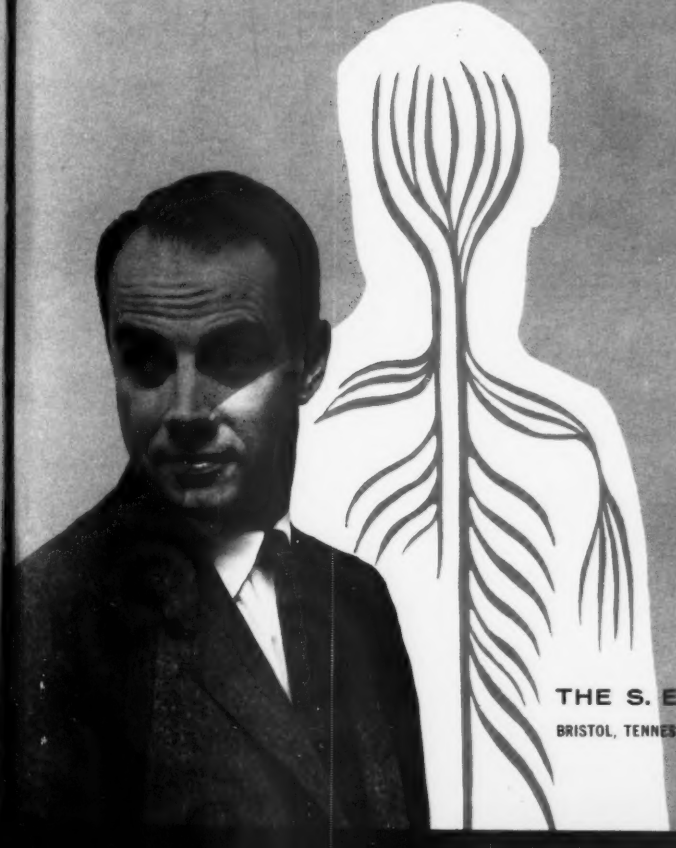

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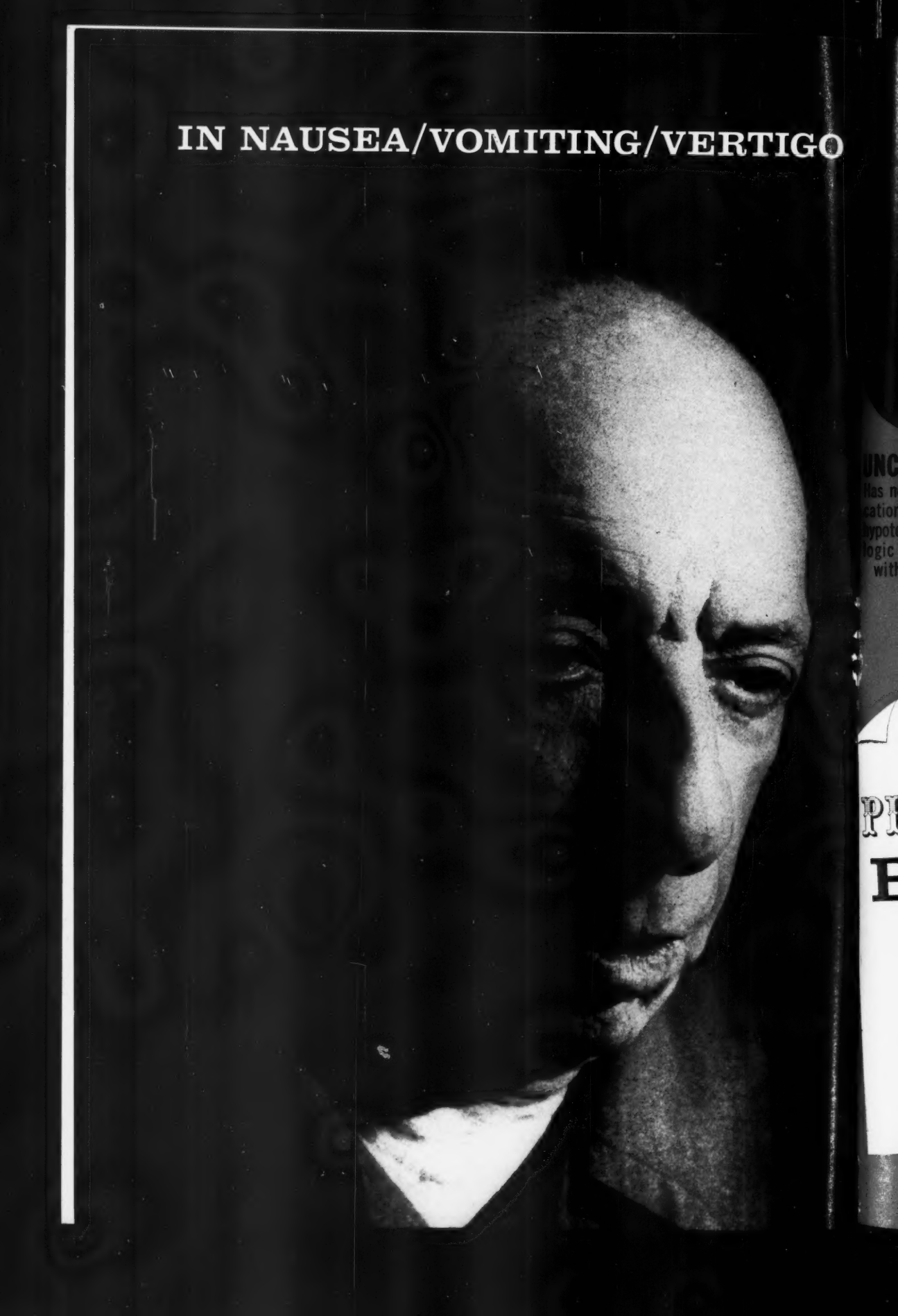

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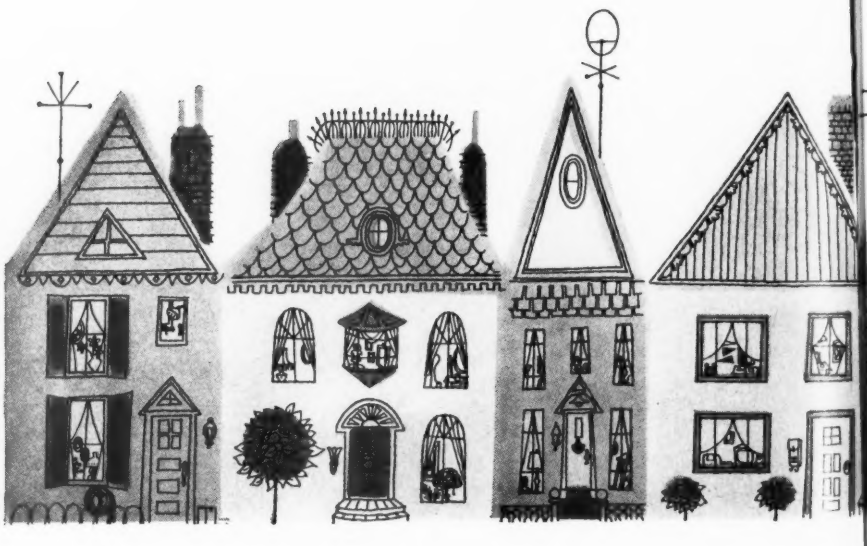
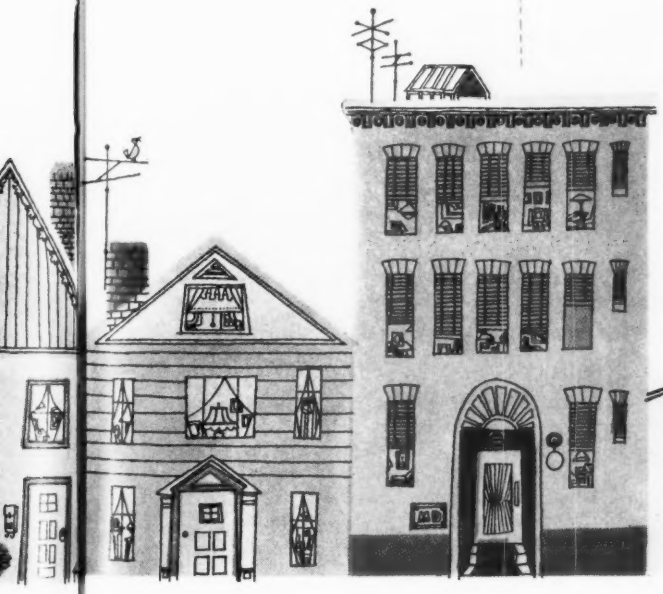
"But, Doctor, I just can't swallow a lot of tablets"



"Little mother, just
ONE
BONADOXIN®
tablet stops morning sickness
(you take it at bedtime)"



The formula tells why Bonadoxin quickly stops nausea and vomiting of pregnancy in 9 out of 10 cases.*

Each tiny Bonadoxin tablet contains:
Meclizine HCl (25 mg.) for antinauseant action
Pyridoxine HCl (50 mg.) for metabolic replacement

More than 60,000,000 tablets prescribed and taken. Toxicity low, tolerance excellent. In bottles of 25 and 100. Usual dose: one tablet at bedtime; severe cases may require another on arising. See PDR, p. 779.

Bonadoxin also effectively relieves nausea and vomiting associated with: anesthesia, radiation sickness, Meniere's syndrome, labyrinthitis, cerebral arteriosclerosis and motion sickness.

ROERIG Rx

New York 17, New York
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

After
Baby Comes

For infant colic, try antispasmodic Bonadoxin Drops... stop colic in 7 out of 8 cases.*

Each cc. contains:
Meclizine 8.33 mg. / Pyridoxine 16.67 mg.
See PDR, p. 779.

*Bibliography available on request.

MI-CEBRIN®... broad vitamin-mineral support to help maintain tissue integrity

"Mere duration of life is not enough," stresses Spies;[1] "... we must devise methods which make old age wait." These, he says, are chiefly dependent on nutrition and the metabolic state. Although nutrition is a problem that involves all essential nutrients, vitamins and minerals play a vital role in the production and maintenance of healthy tissues.

Mi-Cebrin supplies 11 vitamins and 10 minerals in an attractive, easy-to-take tablet. Just one tablet a day will prevent practically all known vitamin-mineral deficiencies. Prescribe Mi-Cebrin as a part of your total effort to extend the *prime of life* of your adult patients.

Mi-Cebrin® (vitamin-mineral supplements, Lilly)

1. Spies, T. D.: The Influence of Nutritional Processes on Aging, South. M. J., *50*:216, 1957.

LILLY VITAMINS..."THE PHYSICIAN'S LINE"

906000

FOR CONCISE INFORMATION ON THE CLINICAL USE OF KANTREX

Q Why should I use KANTREX® Injection* when there are so many other antibiotics available?

A

Because KANTREX Injection is bactericidal to a wide variety of organisms, including many that are highly resistant to the other antibiotics[3,4,10,12,13,17,18,20,21,23,24,25,27,30,33,35,37]

—organisms such as *Staph. aureus, Staph. albus, A. aerogenes, E. coli, H. pertussis, K. pneumoniae, Neisseria* sp., *Shigella, Salmonella* and many strains of *B. proteus.*

Q *But if I use* KANTREX *Injection, won't that help make bacteria resistant to it also?*

Next page, please . . . . . .

* Kanamycin sulfate injection (Bristol)

Q *But if I use* KANTREX *Injection, won't that help make bacteria resistant to it also?*

A A very good question, but it is reassuring to note that in almost two years of clinical use of KANTREX for the treatment of infections for which it is recommended, the emergence of KANTREX-resistant bacterial populations has not been a problem.

Q *My impression is that* KANTREX *is just another neomycin. Isn't that so?*

A Indeed not. The only thing KANTREX and neomycin have in common is a similar antimicrobial spectrum. Otherwise, they're very different: they have different chemical structures; the toxicity of KANTREX is "much less than that of neomycin"[14]; and clinically, KANTREX Injection is practical for systemic administration routinely, while neomycin is not.

Q *You mean that* KANTREX *Injection doesn't have the nephrotoxicity of neomycin?*

A Precisely. It's true that when KANTREX Injection is used, urinary casts – even slight albuminuria or microscopic hematuria – may appear, especially in poorly hydrated patients, but this does not reflect any progressive damage to the kidneys. These signs promptly disappear on adequate hydration or termination of therapy.

Q *Then why do you recommend reduced dosage in patients with renal impairment?*

A Because renal impairment causes an excessive accumulation of KANTREX in the blood and tissues, when usual doses are administered. Since KANTREX Injection is excreted entirely by the kidneys, renal impairment leads

to unnecessarily high and prolonged blood levels; and such excessive concentrations increase the risk of ototoxicity.

Q *Is that why we see reports of patients developing hearing loss during* KANTREX *Injection therapy?*

A Yes. A study of the few reported cases in which patients have suffered impaired hearing will show that in every instance they had pre-existing or concurrent renal impairment, yet received usual or excessive doses of KANTREX Injection. Dosage recommendations for KANTREX Injection emphasize that in patients with renal dysfunction, adequate serum levels can be achieved with a fraction of the dose suggested for patients with normal kidney function – with minimal risk of ototoxicity.

Q *Since urinary tract infections are often accompanied by renal impairment, does that mean I shouldn't use* KANTREX *Injection in such conditions?*

A Not at all. With proper precautions, KANTREX Injection is an excellent drug for the treatment of urinary tract infections, especially those due to *Proteus, A. aerogenes* and *E. coli*, even when renal impairment is present.

Q *What are the "proper precautions" in a patient with impaired renal function?*

A The package literature covers them in detail. First, the daily dose should be reduced in such a patient. Then, if he is going to receive KANTREX Injection for 7 days or more, a pre-treatment audiogram should be done, and it should be repeated at appropriate intervals during therapy. If tinnitus or subjective hearing loss develops, or if followup audiograms show significant loss of high frequency response, KANTREX therapy should be discontinued. However, therapy for 7 days or more

is seldom required because the clinical response to KANTREX Injection is so rapid.

Q *Why do you put so much emphasis on* KANTREX'S *"rapid action"? Every antibiotic I've heard about is supposed to be "rapid acting."*

A There is such an abundance of clinical evidence about "rapid acting" that it takes KANTREX Injection out of the "supposed-to" class.[1,2,3,7,8,9,11,15,16,19,21,22,26,29,32,33] Remember, the effectiveness of KANTREX Injection therapy can usually be appraised in 24 to 36 hours. That's definite evidence of rapid action. In fact, one group of investigators reported that "the rapidity with which bacteria are killed by this agent is reflected by the promptness of the clinical response."[29]

Q *Does* KANTREX *Injection cause blood dyscrasias?*

A In extensive clinical and toxicity studies by numerous investigators, as well as almost two years of general use, not a single instance of such toxicity has been reported.

Q *Can I administer* KANTREX *Injection in any other way than by the intramuscular route?*

A Yes. While it's usually given intramuscularly, other routes are practicable: intravenous, intraperitoneal, by aerosol, and as an irrigating solution. Complete instructions are included in the package insert.

Q *So you think I ought to use* KANTREX *Injection as my first choice antibiotic in staph and gram-negative infections?*

A Yes – because all evidence to date indicates that it is bactericidal against a wide range of organisms... rapid acting... does not encourage development of bacterial resistance... is well tolerated in specified dosage... and has not caused any blood dyscrasias.

KANTREX® CAPSULES

for local gastrointestinal therapy... not for systemic infections

Q *Why can't I use* KANTREX *Capsules for systemic medication?*

A Because there is only negligible absorption of KANTREX from the gastrointestinal tract.[3,5,6,8,28,34] Thus, capsules cannot provide effective blood levels.

Q *Then what are* KANTREX *Capsules used for?*

A Preoperative bowel sterilization, and local treatment of intestinal infections due to kanamycin-sensitive organisms.

Q *I've been using neomycin for preoperative bowel sterilization. Why should I switch to* KANTREX *Capsules?*

A Because KANTREX has been rated as "superior to neomycin" for this purpose.[6] It provides rapid and satisfactory control of coliforms, clostridia, staphylococci and streptococci; yeasts do not proliferate; stool concentrations of the drug are exceptionally high; and nausea, vomiting or intestinal irritation have not been observed.[5,6]

Q *What advantages do* KANTREX *Capsules offer me in the treatment of intestinal infections?*

A A high degree of effectiveness against most of the pathogens responsible for such infections: *Salmonella, Shigella, Staph. aureus, E. coli* and *Endamoeba histolytica.* Moreover, their use has been "remarkably free of any side effects."[31]

KANTREX®

INJECTION KANAMYCIN SULFATE INJECTION

INDICATIONS

Infections due to kanamycin-sensitive organisms, particularly staph or "gram-negatives": genito-urinary infections; skin, soft tissue and post-surgical infections; respiratory tract infections; septicemia and bacteremia; osteomyelitis and periostitis.

DOSAGE: INTRAMUSCULAR ROUTE

Recommended daily dose is 15 mg. per kg. of body weight, in 2 to 4 divided doses.

For intramuscular administration, KANTREX Injection should be injected deeply into the upper outer quadrant of the gluteal muscle.

TOXICITY

When the recommended precautions are followed, the incidence of toxic reactions to KANTREX is low. In well hydrated patients under 45 years of age with normal kidney function, receiving a total dose of 20 Gm. or less of KANTREX, the risk of ototoxic reactions is negligible.

In patients with renal disease and impaired renal function, the daily dose of KANTREX should be reduced in proportion to the degree of impairment to avoid accumulation of the drug in serum and tissues, thus minimizing the possibility of ototoxicity. In such patients, if therapy is expected to last 7 days or more, audiograms should be obtained prior to and during treatment. KANTREX therapy should be stopped if tinnitus or subjective hearing loss develops, or if audiograms show significant loss of high frequency response.

OTHER ROUTES OF ADMINISTRATION

KANTREX should be used by intravenous infusion only when the intramuscular route is impracticable. KANTREX can also be employed for intraperitoneal use, aerosol treatment, and as an irrigating solution. See package insert for directions.

PRECAUTIONS

Use of antibiotics may occasionally result in overgrowth of non-sensitive organisms. If superinfection appears during therapy, appropriate measures should be taken.

SUPPLY

Available in rubber-capped vials as a ready-to-use sterile aqueous solution in two concentrations (stable at room temperature indefinitely):

KANTREX Injection, 0.5 Gm. kanamycin (as sulfate) in 2 ml. volume.
KANTREX Injection, 1.0 Gm. kanamycin (as sulfate) in 3 ml. volume.

CAPSULES (for local gastrointestinal therapy; not for systemic medication)

INDICATIONS AND DOSAGE

For preoperative bowel sterilization: 1.0 Gm. (2 capsules) every hour for 4 hours, followed by 1.0 Gm. (2 capsules) every 6 hours for 36 to 72 hours.

For intestinal infections: Adults: 3.0 to 4.0 Gm. (6 to 8 capsules) per day in divided doses for 5 to 7 days. Infants and children: 50 mg. per kg. per day in 4 to 6 divided doses for 5 to 7 days.

PRECAUTION

Preoperative use of KANTREX Capsules is contraindicated in the presence of intestinal obstruction. Although only negligible amounts of KANTREX are absorbed through intact intestinal mucosa, the possibility of increased absorption from ulcerated or denuded areas should be considered.

SUPPLY

KANTREX Capsules, 0.5 Gm. kanamycin (as sulfate), bottles of 20 and 100.

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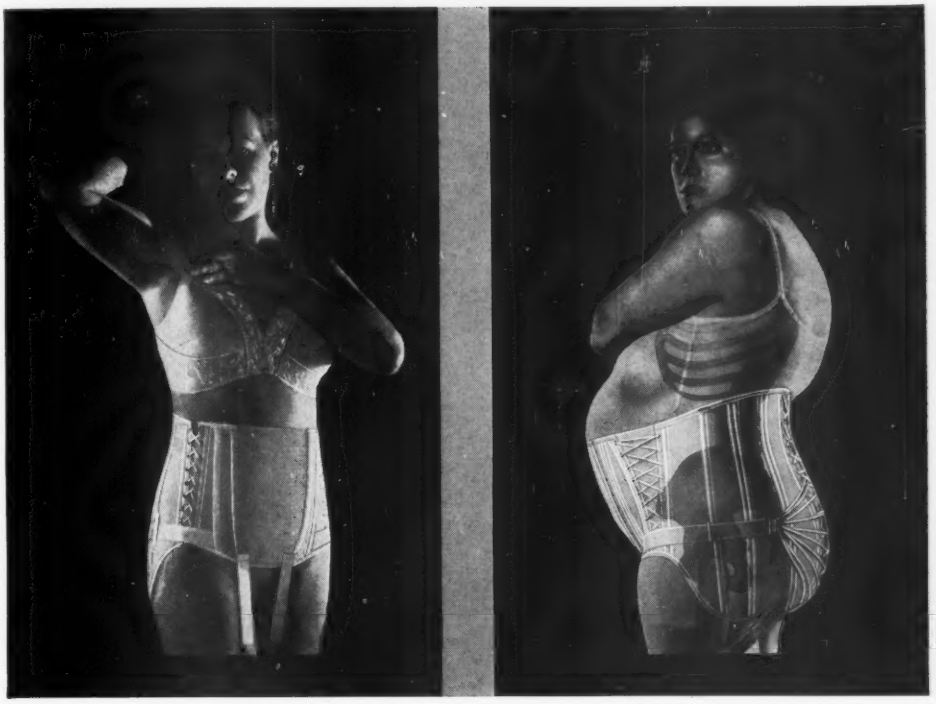
1. Andrieu, G., Monnier, J., and Bourse, R.: Presse Med. 67:718, 1959. 2. Berger, S. H., and Wehrle, P. F.: Ann. N. Y. Acad. Sci. 76:136, 1958. 3. Bunn, P. A., Baltch, A., and Krajnyak, O.: *Ibid.* 76:109, 1958. 4. Bunn, P. A., and Baltch, A.: New Eng. J. Med. 259:659, 1958. 5. Cohn, I., Jr., and Longacre, A. B.: S. G. & O. 108:100, 1959. 6. Cohn, I., Jr.: Ann. N. Y. Acad. Sci. 76:212, 1958. 7. Cronk, G. A., and Naumann, D. E.: *Ibid.* 76:308, 1958. 8. Cronk, G. A., and Naumann, D. E.: J. Lab. & Clin. Med. 53:888, 1959. 9. Davies, F. G.: Ann. N. Y. Acad. Sci. 76:129, 1958. 10. Dougherty, L. J., Seneca, H., and Lattimer, J. K.: Antibiotics Annual 1958-1959, p. 713. 11. Dube, A. H.: Am. Pract. & Digest Treat. 10:1165, 1959. 12. Finegold, S. M., *et al.*: Antibiotics Annual 1958-1959, p. 606. 13. Finegold, S. M., *et al.*: Ann. N. Y. Acad. Sci. 76:319, 1958. 14. Finland, M.: *Ibid.* 76:391, 1958. 15. Finland, M.: Lancet 2:209, 1958. 16. Fujii, R., *et al.*: J. Japan M. A. 39:740, 1958; abst. World-Wide Abst. Gen. Med. 2:28, 1959. 17. Gourevitch, A., Hunt, G. A., and Lein, J.: Ant. & Chemo. 8:149, 1958. 18. Gourevitch, A., *et al.*: Ann. N. Y. Acad. Sci. 76:31, 1958. 19. Greey, P. H., and Wightman, K. J. R.: *Ibid.* 76:224, 1958. 20. Griffith, L. J., and Ostrander, W. E.: Ant. & Chemo. 9:416, 1959. 21. Hewitt, W. L., and Finegold, S. M.: Ann. N. Y. Acad. Sci. 76:122, 1958. 22. High, R. H., Sarria, A., and Huang, N. N.: *Ibid.* 76:289, 1958. 23. Hirsh, H. L.: Sibley Mem. Hosp. Alumni Assn. Bull. 2:16, 1959. 24. Hunt, G. A., and Moses, A. J.: Ann. N. Y. Acad. Sci. 76:81, 1958. 25. Lattimer, J. K., Seneca, H., Zinsser, H. H. and Troc, O.: J.A.M.A. 170:938, 1959. 26. Prigot, A., Shidlovsky, B. A., and Campbell, E. A.: Ann. N. Y. Acad. Sci. 76:204, 1958. 27. Riley, H. D., Jr.: Antibiotics Annual 1958-1959, p. 623. 28. Ruiz Sanchez, F., *et al.*: *Ibid.*, p. 725. 29. Rutenburg, A. M., Koota, G. M., and Schweinburg, F. B.: Ann. N. Y. Acad. Sci. 76:348, 1958. 30. Slotkin, E. A.: Postgrad. Med. 25:433, 1959. 31. Thurman, W. G., and Platou, R. V.: Ann. N. Y. Acad. Sci. 76:230, 1959. 32. Welch, H., *et al.*: *Ibid.* 76:66, 1958. 33. White, A., and Knight, V.: *Ibid.* 76:277, 1958. 34. Yow, E. M.: Practitioner. 182:759, 1959. 35. Yow, E. M., *et al.*: A.M.A. Arch. Int. Med. 102:948, 1958. 36. Yow, M. D., Desmond, M. M., and Nickey, L. N.: J. Ped. 54:409, 1959. 37. Yow, M. D., and Womack, G. K.: Ann. N. Y. Acad. Sci. 76:363, 1958.

Bristol LABORATORIES INC. • Syracuse, New York

CAMP PRENATAL SUPPORTS

scientifically designed for effective supports during pregnancy



Camp prenatal abdominal supports aid the pregnant patient in three ways:

1. **By supporting the abdomen and aiding the abdominal musculature in retaining the developing uterus.**
2. **By supporting the pelvic girdle and decreasing liability of strain on the sacro-iliac joint.**
3. **By supporting the spinal column, thus lessening weariness and backache.**

This **complete,** scientific support brings reports of relief of tension on abdominal muscles and fascia, decrease in appearance of striae gravidarum, symptomatic relief from distress and discomfort of pregnancy and facilitation of return of venous blood from the extremities. In replacing the patient's center of gravity over the supporting joints, the Camp prenatal garment generally relieves strain on muscles on the back and feet.

Camp-trained fitters are ready to give your prenatal patients immediate, expert service according to your specific prescription.

S. H. CAMP and COMPANY CAMP TRADE MARK Jackson, Michigan

. . . get him back on the job sooner

THE DIRECT APPROACH

✓	RHEUMATOID ARTHRITIS
	TRAUMATIC ARTHRITIS
	ACUTE GOUTY ARTHRITIS
	STRAINS AND SPRAINS
	BURSITIS
	FIBROSITIS

to immediate corticosteroid benefits

INJECTION

Decadron®

PHOSPHATE

DEXAMETHASONE 21-PHOSPHATE

- *ready for use immediately*
- *effective immediately*

mg. for mg. the most active steroid in true solution

- in joints or soft tissue—direct action at the site of inflammation
- systemically—rapid relief and prolonged effect —complete solubility affords quick diffusion of the therapeutic dose
- needs no reconstitution . . . no refrigeration
- potency up to 40 times that of hydrocortisone
- passes easily through small-bore needles

Injection DECADRON Phosphate can also be used in other joint diseases or soft-tissue conditions such as osteoarthritis, osteochondritis, "trigger" points (localized painful areas in muscles), tendinitis, whiplash injuries (acute), and muscle trauma. Caution: Steroids should not be given in the presence of tuberculosis, chronic nephritis, acute psychosis, peptic ulcer, or ocular herpes simplex.

DOSAGE AND ADMINISTRATION: Injection DECADRON Phosphate is ready for immediate use intramuscularly or intra-articularly. Dosage varies from 4 mg. or less to 20 mg. or more, depending on the nature and severity of the condition.

NOTE: Do not inject into intervertebral joints.

SUPPLIED: 5 cc. vials with 4 mg. dexamethasone 21-phosphate as the disodium salt per cc.

Literature on Injection DECADRON is available at your request.

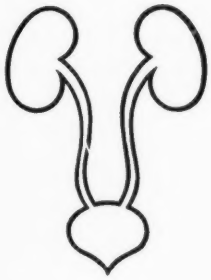
DECADRON is a trademark of Merck & Co., Inc.

MSD MERCK SHARP & DOHME
Division of Merck & Co., Inc., Philadelphia 1, Pa.

from 2 major approaches to urinary tract infections...

ANTIBIOTIC

SULFONAMIDE



...a single approach

VIA TISSUE Cosa-Terramycin provides high, prompt tissue levels of a clinically proven broad-spectrum antibiotic.

VIA URINE Sulfamethizole provides fast-acting, dependable chemotherapy for urine sterilization.

plus phenylazo-diamino-pyridine for swift local analgesia and relief of urinary symptoms.

UROBIOTIC®
Cosa-Terramycin® — sulfonamide — analgesic
CAPSULES

in each capsule: Cosa-Terramycin® (oxytetracycline with glucosamine) 125 mg.; sulfamethizole 250 mg.; phenylazo-diamino-pyridine HCl 50 mg.

dosage: 1 to 2 capsules 4 times daily.

A Professional Information Booklet containing complete details on Urobiotic is available on request.

Pfizer *Science for the world's well-being™*

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EXQUISITE

is the word for it

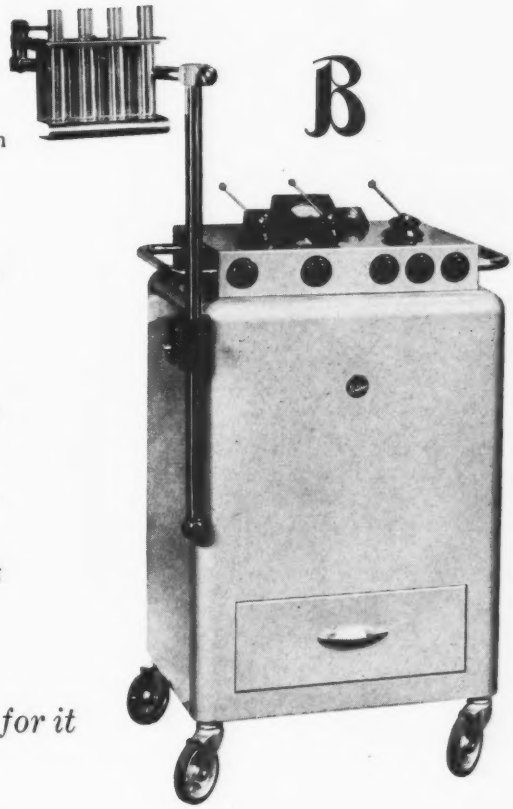
The Birtcher *Personally Certified*

ELECTROSECTILIS

Initial incision may be made through the skin with speed, delicacy and full assurance of first intention healing. Operation with finesse is assured even when employed to activate a 33Fr.–15/1000 gauge loop as employed at times by the urologist.

Exsanguine coagulation with pin-point precision, without massive blasting and risk of slough and secondary hemorrhage is the keynote.

The "Personally Certified" is in daily use in hundreds of major Army, Navy and V.A. Hospitals, and in thousands of great hospitals from South Africa to Europe, from Japan and China to Canada, from Alaska to South America, and in every state in the Union. Thousands have given yeoman service daily for 11 full years without requiring more service than a mere 15 minute adjustment.



Yes, Exquisite is the word for it

For descriptives write . . .

THE BIRTCHER CORPORATION

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4371 Valley Boulevard, Los Angeles 32, California

The entire instrument and the special Explosion Proof Footswitch have been tested by, and bear the seal of, Underwriters' Laboratories.

NEW PERMITIL®

Fluphenazine dihydrochloride

the promise of

in everyday office practice

safely control the "target symptoms"
of emotional stress with the
smallest effective dosage (0.25 mg. b.i.d.)
of any neuroleptic* agent

*neuroleptic–

"The term 'neuroleptic' implies a specific effect of a pharmacologic agent on the nervous system. It refers to a mode of action on affective tension that distinguishes this response from that to hypnotic drugs. The terms 'ataraxics' and 'tranquilizers' are descriptively impressive, but fail to convey what seems psychopharmacologically unique."[1]

the premise

Emotional tension states, psychosomatic disorders and similar neuroses constitute a major portion of the clinical conditions seen today in everyday office practice. Whether the emotional stress is in the form of a behavioral disturbance characterized by anxiety, anxiety accompanying specific organic disorders or chronic conditions in which anxiety is a contributing factor, the aim in therapy is the same: to alleviate emotional stress and enable the patient to cope with life's problems more effectively and to live more comfortably.

The choice of an agent to overcome the patient's particular "target symptoms" of emotional stress, without impairing alertness or productivity, or producing undesirable reactions, is often a difficult and haphazard task. Yet, one may be guided by the fact that there is a correlation between the dosage of a phenothiazine derivative and the frequency and the type of side effects it causes, ***the less of the drug needed to achieve therapeutic results, the less likely are side effects.*** Thus, the lower the effective dosage of a phenothiazine derivative, the lower the incidence of unwanted side reactions and, conversely, the higher the level of therapeutic response.

Now, with PERMITIL, the physician may prescribe a neuroleptic anti-anxiety agent of extraordinary potency and effectiveness, at unprecedented low dosage, with minimal side effects—features that markedly distinguish this compound from other anti-anxiety agents.

the promise

Extensive clinical studies have established important psychopharmacologic advantages for PERMITIL. The effective dosage of PERMITIL *(0.25 mg.* b.i.d.) is the lowest safe dosage of any anti-anxiety agent. Side effects associated with dosage not exceeding 1 mg. per day have been uncommon and transitory.

Unlike other phenothiazines, PERMITIL alleviates symptoms of anxiety, tension, agitation and emotional unrest *without* depressant effect, impaired alertness or slowed intellectual function.

Furthermore, anxiety-induced symptoms of apathy, indifference, listlessness, reduced initiative and chronic emotional fatigue (often refractory to other phenothiazines) frequently respond to administration of PERMITIL. Thus, *a significantly wider spectrum of "target symptoms"* amenable to therapy is an outstanding property of PERMITIL.

Onset of action with PERMITIL is rapid and patients soon become more relaxed and less tense. The patient regains a more confident outlook and normal drive is restored.

PERMITIL has an inherently long duration of effect. This makes possible a particularly convenient and easy-to-remember schedule of morning and evening dosage.

The promise of PERMITIL in everyday office practice, then, is the more effective control of the "target symptoms" of emotional stress with the lowest safe dosage of any anti-anxiety agent.

PERMITIL®

to fit the promise to your office practice

"The pharmacologic management of psychiatric disorders challenges the therapeutic acumen of the physician. He must choose a drug which will produce remission as quickly as possible with the least risk."[2] In this regard, PERMITIL represents an advance over its predecessors[2] because of its higher level of therapeutic response and low order of side reactions.

The adjunctive use of PERMITIL by the family physician enables him to provide effective pharmacotherapy for many of the emotional symptoms which constitute a major portion of patient disability in everyday office practice.

The Areas of Usefulness for PERMITIL:

- Behavioral disturbances characterized by anxiety, tension, apprehension and instability, as well as depressive symptoms associated with anxiety states
- Emotional stress accompanying organic disorders and complicating recovery from, or acceptance of, the underlying condition
- Chronic disorders in which anxiety and stress are contributing factors, e.g., gastrointestinal dysfunctions, neurodermatitis, asthma, premenstrual tension, arthritis, hypertension and tension headache

How to Prescribe PERMITIL:

PERMITIL has an inherently long duration of effect so that it need be given only twice a day making possible an easy-to-remember morning and evening dosage program. The lowest dose of PERMITIL that will produce the desired clinical effect should be used.

The recommended dose for most adults is one 0.25 mg. tablet twice a day

This may be increased to two 0.25 mg. tablets twice a day if required. Total daily dosage in excess of 1 mg. should be employed only in patients with relatively severe symptoms who have had a trial of lower dosages first that were well tolerated but were only partially effective. In such patients, the total daily dose may be increased to a maximum of 2 mg., given in divided amounts. (Dosage for children has not been established.)

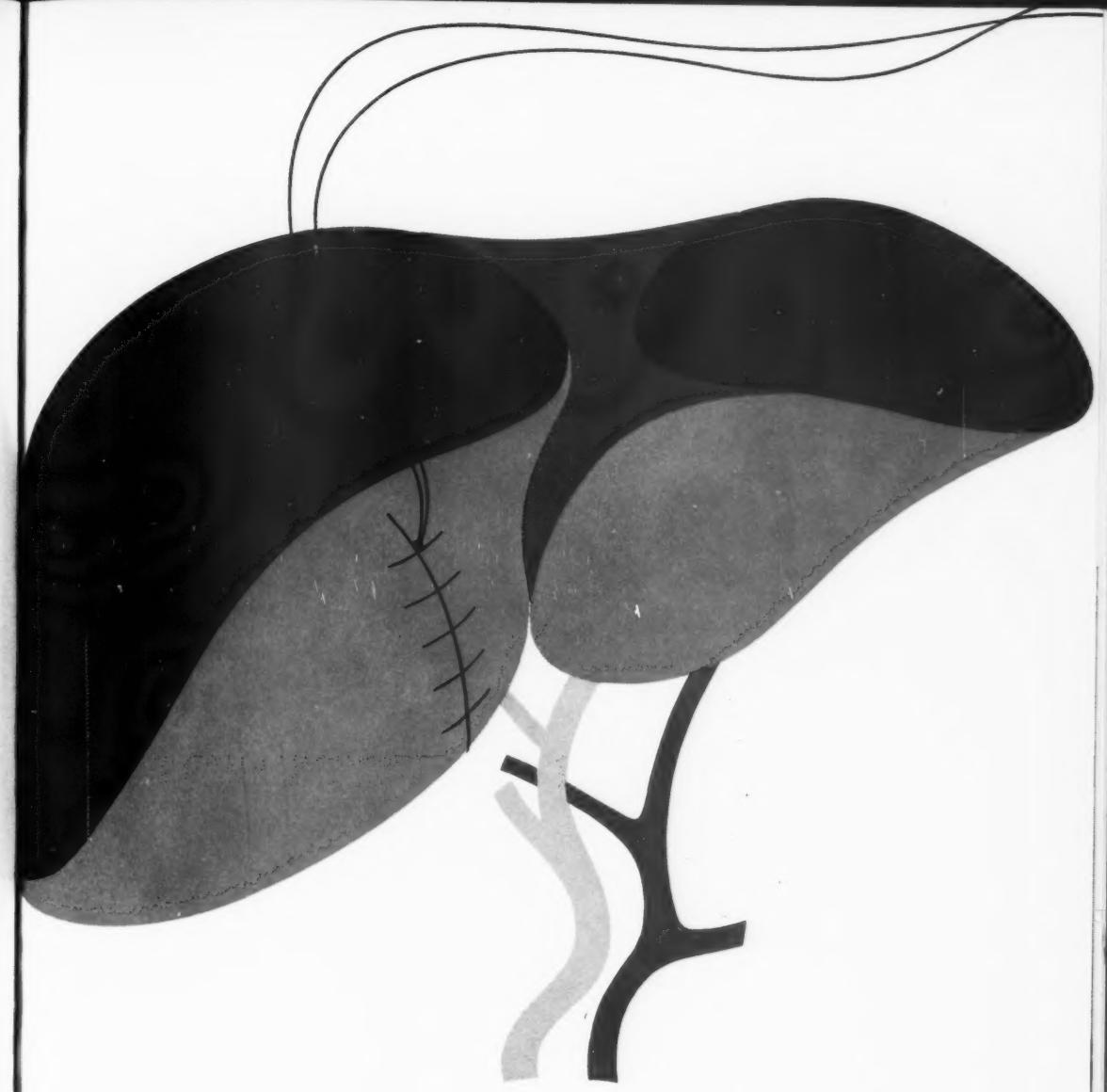
Side Effects—Infrequent; Contraindications—Minimal:

At the recommended dosage of PERMITIL, side effects have been observed infrequently or not at all. PERMITIL, as with other phenothiazines, is contraindicated in severely depressed states.

Available in Tablets of 0.25 mg.; bottles of 50 and 500.

References: 1. Freyhan, F. A.: Psychopharmacology Frontiers, Boston, Little, Brown and Co., 1959, p. 7. 2. Ayd, F. J.: The current status of major tranquilizers, in press.

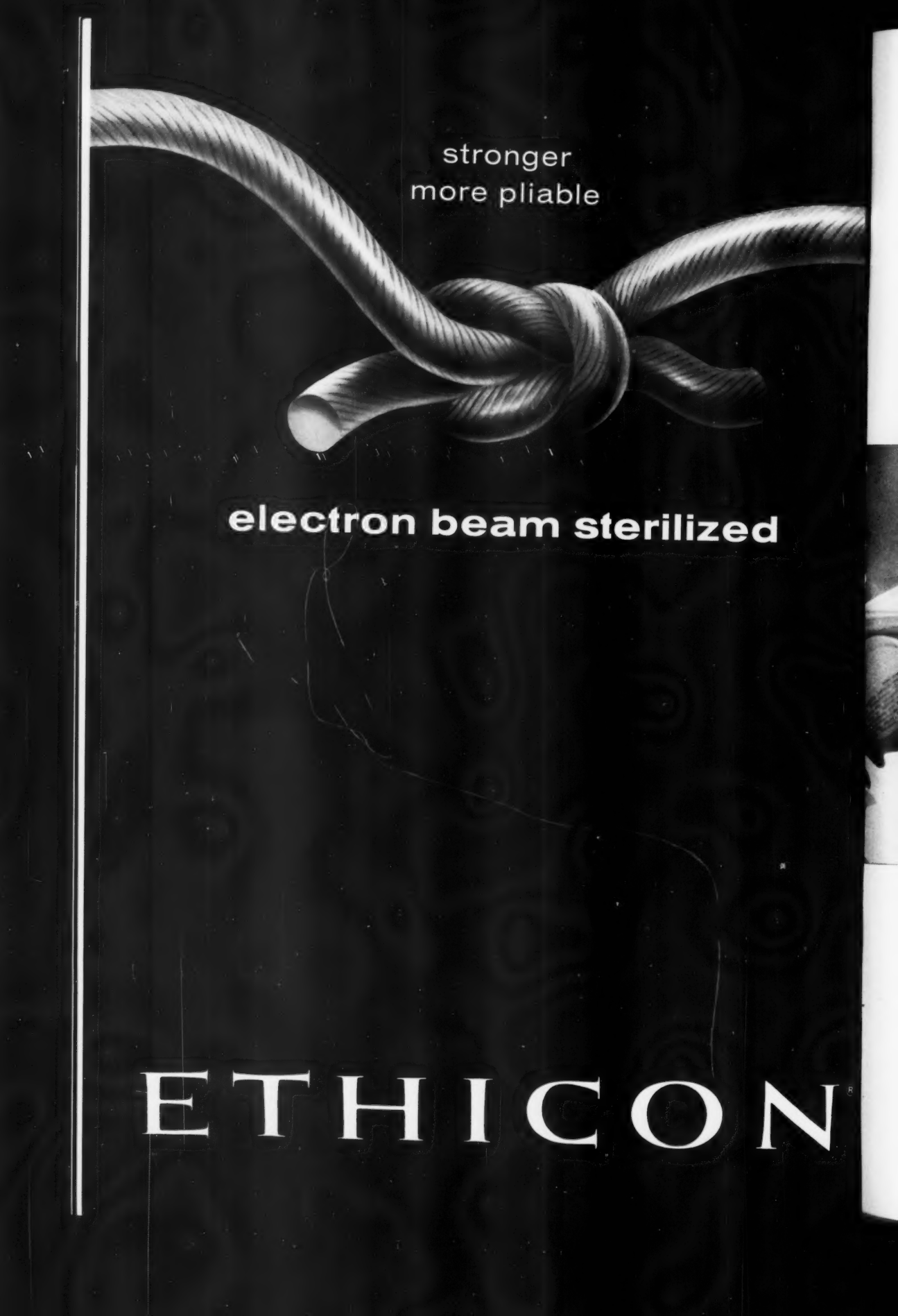
White's WHITE LABORATORIES, INC., *Kenilworth, New Jersey*



advancing with surgery

ETHICON®

sutures


stronger
more pliable
electron beam sterilized
ETHICON®

In a recent placebo-controlled study of 112 patients complaining of nausea and vomiting of pregnancy, Moessner[1] reports 94 per cent relief of symptoms with PROZINE. Optimum dosage was low, side-effects notably infrequent and mild.

PROZINE not only exerts a potent action upon the vomiting mechanism itself, but also controls apprehension and agitation as well as motor excitability by acting on both the hypothalamic and thalamic areas of the brain. PROZINE offers effective therapy in purely psychic conditions and in psychic conditions resulting from, or contributing to, organic disease.

1. Moessner, G.F.: To be Published, Western J. Surg.

Gravida I, Nausea and Vomiting 0

Affects the thalamic and hypothalamic areas of the brain

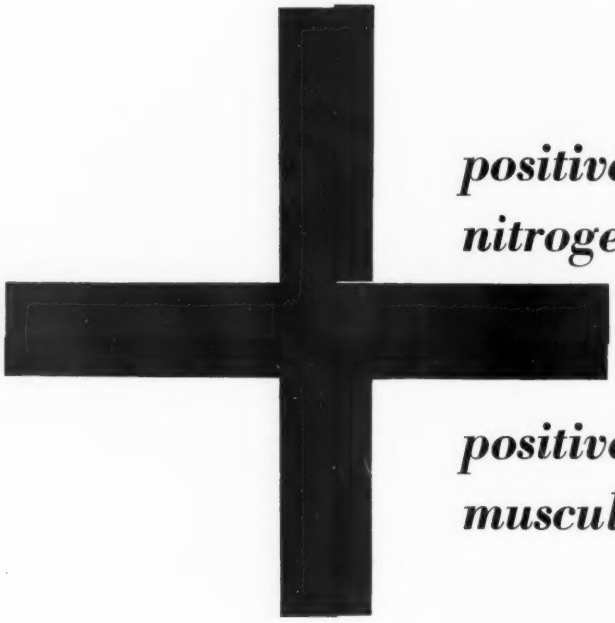
PROZINE*

meprobamate and promazine hydrochloride, Wyeth

SPECIFIC CONTROL THROUGH DUAL ACTION

Wyeth
Philadelphia 1, Pa.

*Trademark



positive
nitrogen balance

positive
muscular growth,

positive, objective gains fo ou

DURABOLIN, *a new, well-tolerated, long-acting biologic stimulant,* has demo nefits strated dramatically that the progress of many negative clinical conditio aling, can be halted or reversed. In more than three years of clinical study in Euro lliative Canada and the United States, positive *measurable* benefits have been induc after even short-term DURABOLIN therapy.

DURABOLIN (nandrolone phenpropionate, injection, Organon) acts as a pote tissue-builder by rapid establishment of a positive nitrogen balance throu more efficient utilization of dietary protein. The weight gain resulting fr urem marked appetite improvement takes the form of solid, lean tissue witho edema.

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Nandrolone phenpropionate injection, Organon

for our patients' well-being

nefits in disorders such as osteoporosis, osteogenesis imperfecta, and slow-aling, uncomplicated fractures. These actions make DURABOLIN a valuable lliative in inoperable mammary cancer with skeletal metastases.

URABOLIN is also indicated as an adjunct to chemo-therapeutic or surgical easures in which a catabolic state has been induced, e.g., during long-term rticosteroid regimens, to prevent excessive nitrogen loss following major erations, and to reduce the serum level of nitrogenous waste products uremia.

nlike most other anabolic steroids, DURABOLIN ordinarily does not induce asculinization when administered in proper doses, nor has there been any idence of progestational activity, hepatic damage, or renal blockage.

URABOLIN (nandrolone phenpropionate, 25 mg./cc. of sesame oil) is sup-ed in 1-cc. ampuls and 5-cc. vials. Recommended adult dose: 25 mg. (1-cc.) ce weekly by intramuscular injection, or 50 mg., i.m., every second week. alf these amounts are recommended for children.

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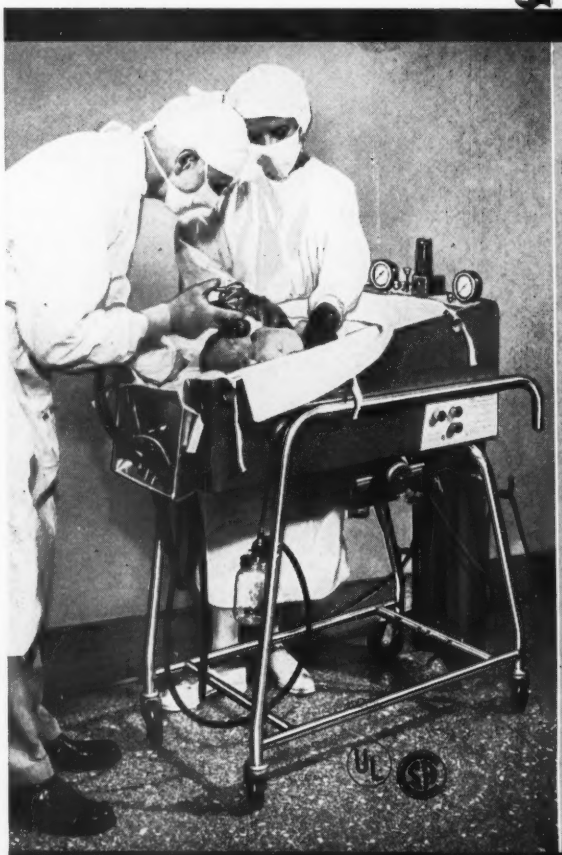

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is **safe** for use in Class I, Group C anesthetizing areas

- Furnishes oxygen intermittently under positive pressure
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Promethazine Hydrochloride and Meperidine Hydrochloride, Wyeth

MEPERGAN provides the analgesia of meperidine augmented by the values of promethazine. These include the allaying of apprehension, the control of nausea and vomiting, the potentiation of barbiturates and narcotics, and the facilitation of anesthesia. MEPERGAN is useful in all forms of surgery. It may be used preoperatively for preparatory medication, during surgery as an adjunct to anesthesia, and postoperatively to control pain. Widespread clinical experience points to MEPERGAN's 1:1 ratio of promethazine and meperidine to be most satisfactory for most patients.

See package circular for complete information on use of MEPERGAN.

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a logical combination in appetite control

BAMADEX®

meprobamate with dextro-amphetamine sulfate LEDERLE

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meprobamate eases tensions of dieting

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d-amphetamine depresses appetite and elevates mood

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...without overstimulation

...without insomnia

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Each coated tablet (pink) contains:
d-amphetamine sulfate .... 5 mg.
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Dosage: One tablet taken one-half to one hour before each meal.

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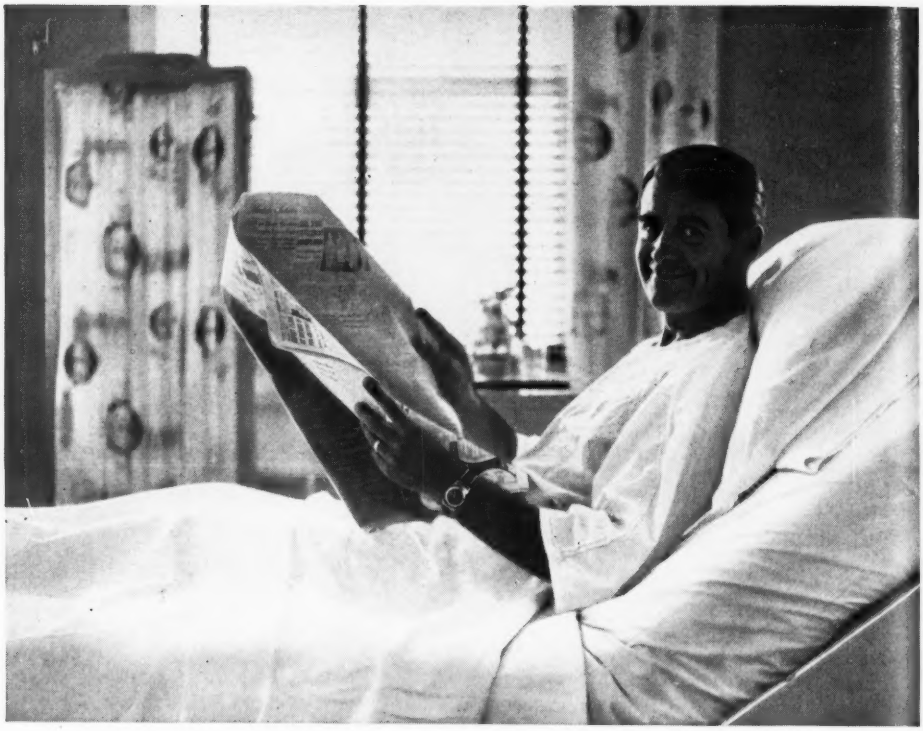

Lessened postoperative vomiting with

MORNIDINE®

- **Low dosage**
- **Specific action on the vomiting center**
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- **Parenteral and tablet forms**

Mornidine (brand of pipamazine), a product of Searle Research, offers distinct advantages in the treatment of postoperative nausea and vomiting. Its low dosage and selective action on the vomiting center combine a high degree of therapeutic effectiveness with greater safety and a low incidence of side effects.

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With Levophed "... necessary surgical procedures were attempted which could not otherwise have been done."[1] "... the most potent and fastest acting of the vasopressor agents."[2]

References: 1. Fremont, R. E.; Luger, N. M.; Surks, S. N., and Kleinman, A.: A.M.A. Arch. Surg. 68:44, Jan., 1954. 2. Agress, C. M., and Binder, M. J.: Am. Heart J. 54:458, Sept., 1957.

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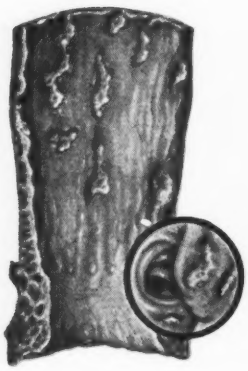

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Supplied: Suppositories, boxes of 12. Each suppository contains 10 mg. hydrocortisone acetate, 15 mg. extract belladonna (0.19 mg. equiv. total alkaloids), 3 mg. ephedrine sulfate, zinc oxide, boric acid, bismuth oxyiodide, bismuth subcarbonate, and balsam peru in an oleaginous base.

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Rectal Suppositories with Hydrocortisone, Wyeth

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whenever there is inflammation, swelling, pain

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Tablets

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conditions for a fast comeback...

as in acute hemorrhoids...

SUNDAY, 9 A.M.: VARIDASE for painful thrombotic hemorrhoid. 2:30 P.M.: pain greatly reduced, less swelling and inflammation.

MONDAY: size down to small tab; acute inflammation disappeared.*

VARIDASE activates natural fibrinolytic factors, to limit undesirable inflammatory response and speed healing.

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Supplied in two potencies for dosage flexibility:

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Both potencies in bottles of 60.

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In minutes, Milprem starts to ease anxiety and depression. It relieves insomnia, relaxes tense muscles; alleviates low back pain and tension headache. As the patient continues on Milprem, the replacement of estrogens checks hot flushes and other physical symptoms.

Easy dosage schedule: One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.

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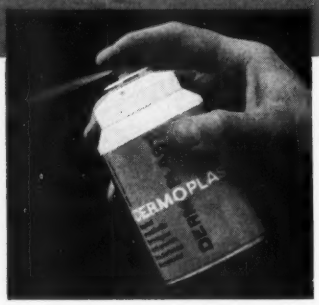
DERMOPLAST®

AEROSOL SPRAY

SOOTHING TOPICAL ANESTHETIC • BACTERICIDAL • FUNGICIDAL

APPLIED WITHOUT TOUCHING THE INVOLVED SENSITIVE AREAS—*Immediate relief of pain and itching is experienced*



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Available in 3 sizes:

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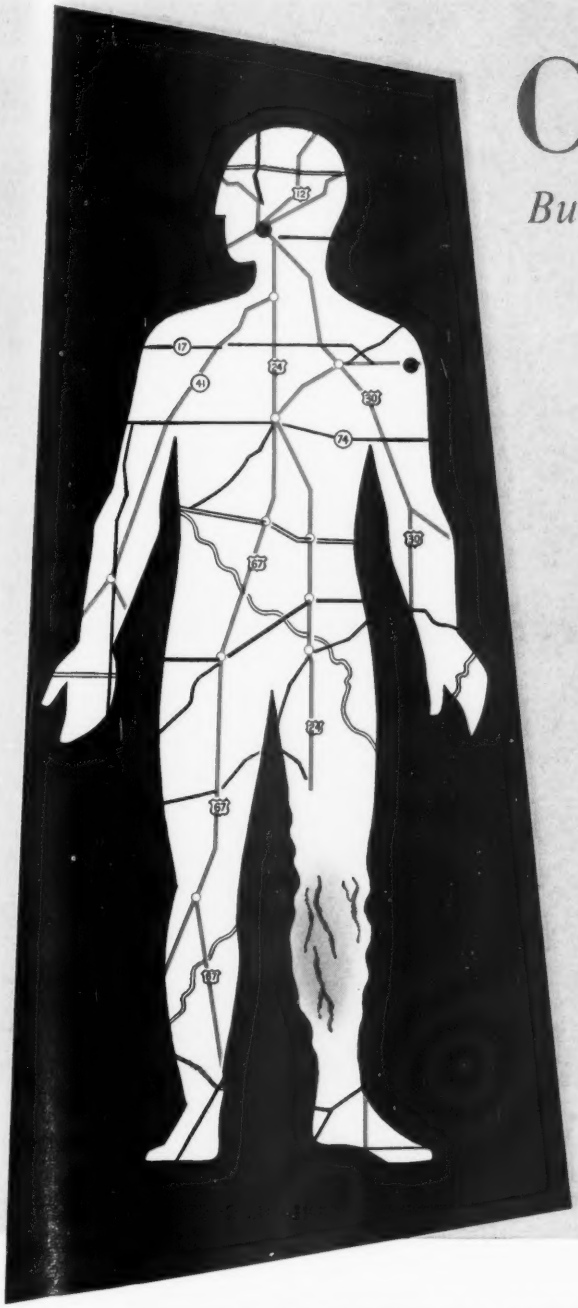

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in surgical conditions
controls inflammation,
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Chymar is remarkably effective in control of reactions to surgical procedures. It accelerates absorption of blood extravasates and edema, relieves pain and expedites the healing process because local circulation is improved. The side effects that have been observed with steroid-type anti-inflammatory agents do not occur with Chymar.

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*Used in plastic surgery, "The results were remarkable . . . total absence of bruising or swelling . . ."**

*Moore, F.T.: Brit. J. Plast. Surg. *11*:335, 1959.

CHYMAR *Buccal* Crystallized chymotrypsin in a tablet formulated for buccal absorption. Bottles of 24 tablets. Enzymatic activity, 10,000 Armour Units per tablet.

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FOR ANXIETY—particularly when expressed as apathy, listlessness and emotional fatigue

TYPICAL PRESENTING SYMPTOMS

loss of normal drive
inability to concentrate or work effectively
indecisiveness
irritability
crying spells
insomnia
anorexia
vague fears
undue preoccupation with somatic complaints
wide swings of mood
generalized discomfort
headaches
dizziness
palpitations
hyperventilation
epigastric distress

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1 mg. STELAZINE* TABLETS

brand of trifluoperazine

'Stelazine' is unique because it not only relieves agitation and tension, but also relieves apathy, listlessness and emotional fatigue resulting from anxiety states.

Other noteworthy characteristics of 'Stelazine', brought out in clinical studies in over 12,000 patients, are:

* effectiveness where other agents fail
* notable lack of troublesome side effects
* fast therapeutic response with very low doses
* convenient b.i.d. administration

"THE INDIFFERENCE WHICH OCCURS COMMONLY WITH OTHER TRANQUILIZERS WAS ABSENT."[1]

This observation about 'Stelazine' points to what may be one of the most important and distinguishing characteristics of the drug—that is, 'Stelazine', while relieving emotional distress, does not "tranquilize" your patients out of normal activity or normal aims.

AVAILABLE for use in everyday practice—1 mg. tablets, in bottles of 50 and 500. Literature available on request. Smith Kline & French Laboratories, Philadelphia.

REFERENCES: 1. Gearren, J.B.: Dis. Nerv. System *20*:66 (Feb.) 1959. 2. Margolis, E.J.; Pauley, W.G.; Cauffman, W.J., and Gregg, P.C.: Scientific Exhibit at the 12th Clinical Meeting of the American Medical Association, Minneapolis, Minn., Dec. 2-5, 1958. 3. Phillips, F.J., and Shoemaker, D.M.: *ibid.* 4. Ayd, F.J., Jr.: Clin. Med. 6:387 (Mar.) 1959.

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SPRAINED BACK

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TRAUMATIC STRAINS AND BRUISES

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■ Exhibits unusual analgesic properties, different from those of any other drug ■ Specific and superior in relief of SOMAtic pain ■ Modifies central perception of pain without abolishing natural defense reflexes ■ Relaxes abnormal tension of skeletal muscle

SOMA™

N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate

■ More specific than salicylates ■ Less drastic than steroids ■ More effective than muscle relaxants

SOMA has an unique analgesic action. It apparently modifies central pain perception without abolishing peripheral pain reflexes. SOMA is particularly effective in relieving joint pain. Patients say that they feel better and sleep better with SOMA than with any previously used analgesic, sedative or relaxant drug.
SOMA also relaxes muscle hypertonia, with its stresses on related joints, ligaments and skeletal structures.

ACTS FAST. Pain-relieving and relaxant effects start in 30 minutes and last 6 hours.

NOTABLY SAFE. Toxicity of SOMA is extremely low. No effects on liver, endocrine system, blood pressure, blood picture or urine have been reported. Some patients may become sleepy on high dosage.

EASY TO USE. Usual adult dose is one 350 mg. tablet 3 times daily and at bedtime.

SUPPLIED: Bottles of 50 white sugar-coated 350 mg. tablets.
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1. Spies, T. D.: J. A. M. A. 167:675 (June 7) 1958.

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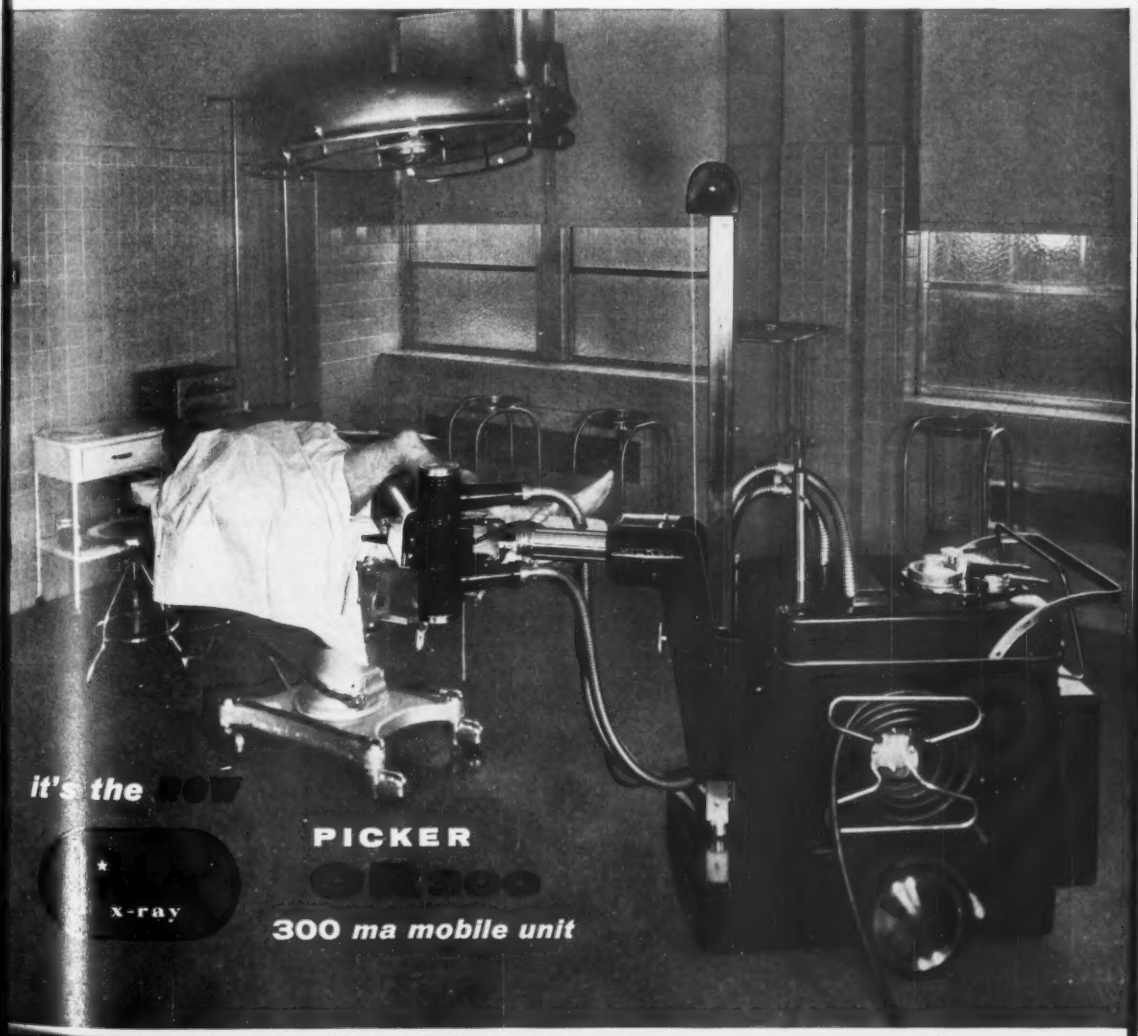
Every room on the O.R. floor can now enjoy high-power x-ray facilities *fully equivalent to those of the regular x-ray department.* Simply wheel the Picker OR 300 Mobile Unit to whichever room requires x-ray, plug it in, and you're all set for the job. Completely self-contained: there's nothing to install in the several rooms except power outlets to run the machine. Safe to operate in explosive atmospheres, it permits use of any gaseous anesthetic. Get the facts about this remarkable apparatus from your local Picker representative.



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MYOCARDIAL INFARCTION

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ARAMINE "Metaraminol combines strong pressor effect with myocardial-stimulating action . . ."[1]

ARAMINE can be administered for balanced pressor, myocardium-stimulating effect by any desired route—intravenous, intramuscular or subcutaneous—with no reported tissue slough and with minimal risk of causing arrythmias. Repeated injections of ARAMINE appear to elicit no tachyphylactic response.

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1. Selzer, A. and Rytand, D.A.: COUNCIL ON DRUGS, Report to Council J.A.M.A. 168:762, (Oct. 11) 1958.

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FOR SAFER, SIMPLER ECG MONITORING DURING SURGERY...

Because Sanborn Company designed the mobile Model 169A-OR Viso-Scope specifically for operating room use — to provide members of the surgical team with instantaneous visual presentation of the patient's electrocardiogram and other cardiovascular events — emphasis has been placed on three major features: *safety*, *accuracy*, and *convenience* of operation.

From the standpoint of safety, the Viso-Scope is the *only* ECG oscilloscope-amplifier unit listed by Underwriters Laboratories as safe for use in the presence of explosive anesthetic gases (Class I, Group C, Hazardous Locations). Waveform accuracy and clarity of presentation are achieved by a bright amber fluorescent image of four seconds duration, displayed on a five inch diameter, long-persistence screen; an illuminated reference scale on the screen permits rapid estimation of the waveform's duration, magnitude, and rate of occurrence. Easy, convenient operation is assured with the Viso-Scope's yoke-mounted, tilting viewing unit; a front panel selector switch for instant change of leads; sweep speed selector switch which permits 25, 50 or 100 mm/second sweeps; simple controls for brightness of scale and trace, focus, and enlargement of a trace of particular interest.

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The Sanborn Model 169A-OR Viso-Scope is the only oscilloscope-amplifier listed by Underwriters Laboratories as safe for use in the presence of explosive anesthetic gases.

Striking relief
from LOW BACK PAIN
and DYSMENORRHEA
THE FIRST TRUE "TRANQUILAXANT"
Trancopal

Here is wha you can expec when you prescrib

Case Profile*

A 28-year-old married woman, a secretary in a booking agency, complained of severe and consistent pain and cramps in the abdomen during her menstrual periods. Psychologically, she described the first two days as "climbing the walls." Menarche occurred at age 13. She has a regular twenty-eight day menstrual cycle and a four day menstrual period.

Trancopal was given in a dose of 100 mg. four times a day for the first two days of the four day period. In addition to the relief of the dysmenorrhea she also noticed disappearance of a "bloated feeling" that had previously annoyed her. She has now been treated with Trancopal for one and one-half years with excellent results. Other medication, such as codeine or aspirin with codeine, had relieved the pain, but the patient had had to stay home. Because her father is a physician, many commercial preparations had been tried prior to Trancopal, but no success had been achieved.

Before taking Trancopal this patient missed one day of work every month. For the past year and a half she has not missed a day because of dysmenorrhea.

for dysmenorrhea
and premenstrual tension

THE FIRST TRUE "TRANQUILAXANT"

Trancopal®

for low back pain

Case Profile*

A 42-year-old truck driver and mover injured his back while moving a piano. The pain radiated from the sacral region down to the region of the Achilles tendon on the right side. X-rays for ruptured disc revealed nothing pertinent. The day of the injury he was given Trancopal immediately after the physical examination. Although 100 to 200 mg. three times a day were prescribed, the patient on his own responsibility increased the dosage of Trancopal to 400 mg. three times a day. This dosage was continued for three days and then gradually reduced over a ten day period. During this time, the patient continued to drive his truck. The muscle spasm was completely controlled and no apparent side effects were noted.

For the past six months, the patient has continued to take Trancopal 100 to 200 mg. as needed for muscle spasm, particularly during strenuous days.

**Clinical Reports on file at the Department of Medical Research, Winthrop Laboratories.*

Turn page for complete listings of Indications and Dosage.

THE FIRST TRUE "TRANQUILAXANT"

Trancopal

potent MUSCLE RELAXANT

effective TRANQUILIZER

- In musculoskeletal disorders, effective in 91 per cent of patients.[1]
- In anxiety and tension states, effective in 89 per cent of patients.[1]
- Low incidence of side effects (2.3 per cent of patients). Blood pressure, pulse rate, respiration and digestive processes are unaffected by therapeutic dosage. It does not affect the hematopoietic system or liver and kidney function.
- No gastric irritation. Can be taken before meals.
- No clouding of consciousness, no euphoria or depression.

Indications [1-6]

Musculoskeletal:

Low back pain (lumbago, etc.)
Neck pain (torticollis)
Bursitis
Rheumatoid arthritis
Osteoarthritis
Disc syndrome
Fibrositis
Ankle sprain, tennis elbow
Myositis
Postoperative muscle spasm

Psychogenic:

Anxiety and tension states
Dysmenorrhea
Premenstrual tension
Asthma
Angina pectoris
Alcoholism

Now available in two strengths:

Trancopal Caplets®,
100 mg. (peach colored, scored), bottles of 100.

NEW STRENGTH

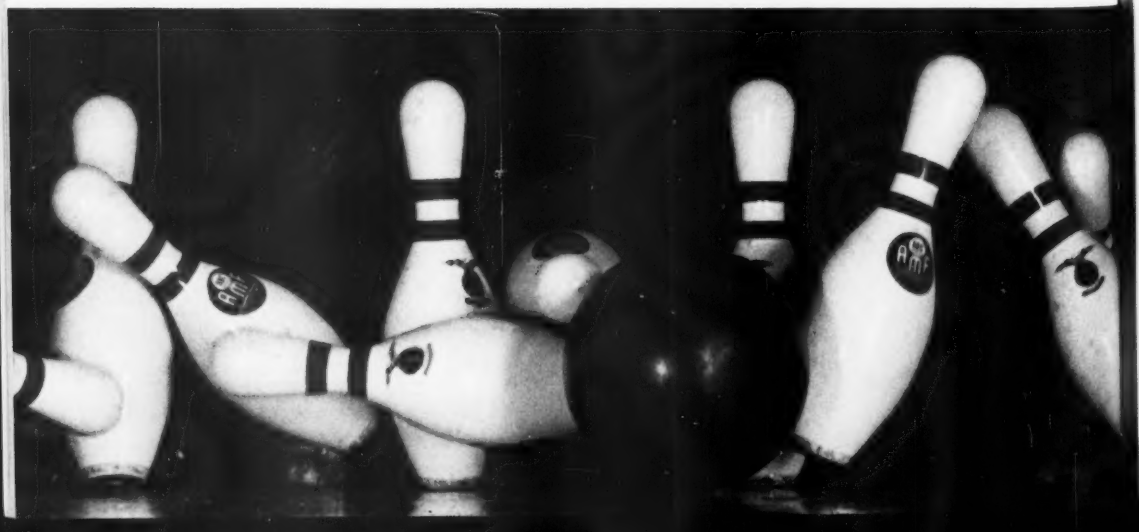
Trancopal Caplets,
200 mg. (green colored, scored), bottles of 100.

Dosage: Adults, 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in from fifteen to thirty minutes and lasts from four to six hours.

Winthrop LABORATORIES
New York 18, N. Y.

References: 1. Collective Study, Department of Medical Research, Winthrop Laboratories. 2. Lichtman, A. L.: New developments in muscle relaxant therapy, *Kentucky Acad. Gen. Pract. J.* 4:28, Oct., 1958. 3. Lichtman, A. L.: Relief of muscle spasm with a new central muscle relaxant, chlormezanone (Trancopal), Scientific Exhibit, Meeting of the International College of Surgeons, Miami Beach, Fla., Jan. 4-7, 1959. 4. Ganz, S. E.: Clinical evaluation of a new muscle relaxant (chlormethazanone), *J. Indiana M. A.* 52:1134, July, 1959. 5. Mullin, W. G., and Epifano, Leonard: Chlormezanone, a tranquilizing agent with potent skeletal muscle relaxant properties, *Am. Pract. Digest Treat.* 10:1743, Oct., 1959. 6. Shanaphy, J. F.: Chlormezanone (Trancopal) in the treatment of dysmenorrhea; a preliminary report, *Current Therap. Res.* 1:59, Oct., 1959.

Trancopal (brand of chlormezanone) and Caplets, trademarks reg. U.S. Pat. Off. 1408M Printed in U.S.A.



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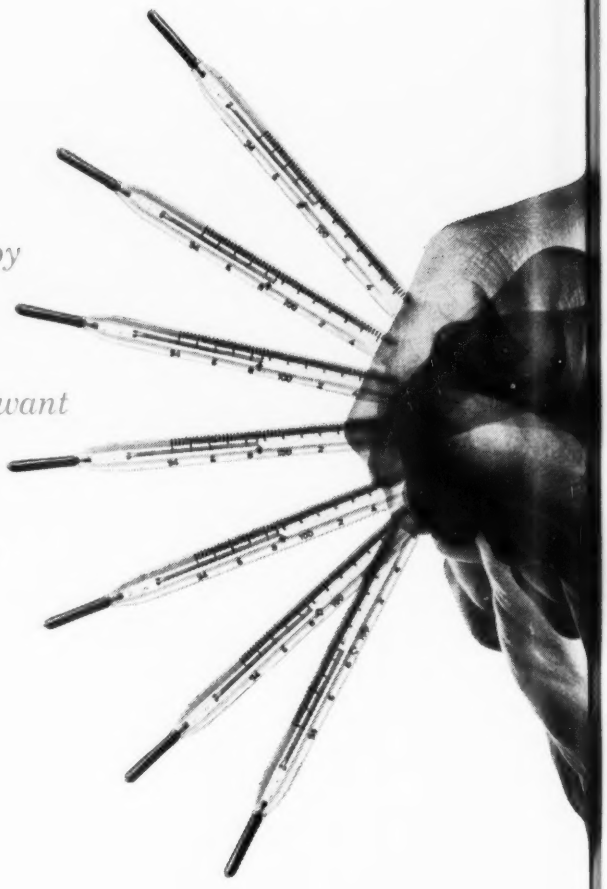

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1. Peck, F.B., Jr., and Griffith, R.S.: Antibiotics Annual 1957-1958, Medical Encyclopedia, Inc., p. 1004. 2. Wright, W.W., and Welch, H.: Antibiotic Med. *5*:139 (Feb.) 1958.

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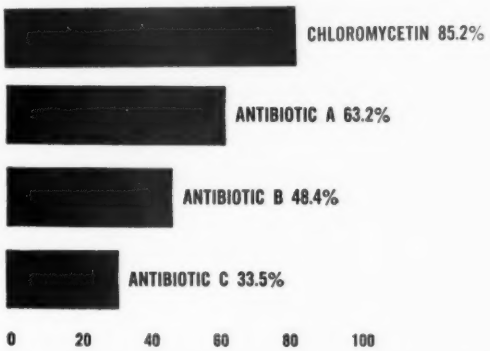

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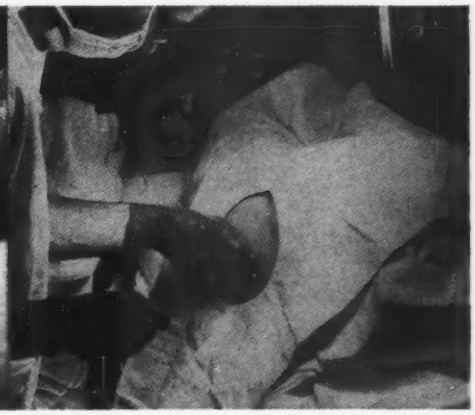

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references: 1. Current Researches in Anesth. & Analges. 33:275, July-August 1954. 2. J. Urol. 72:266, August 1954.
3. Anesthesiology 16:386, May 1955. 4. Western J. Surg., Gynec. & Obst. 59:533, October 1951.

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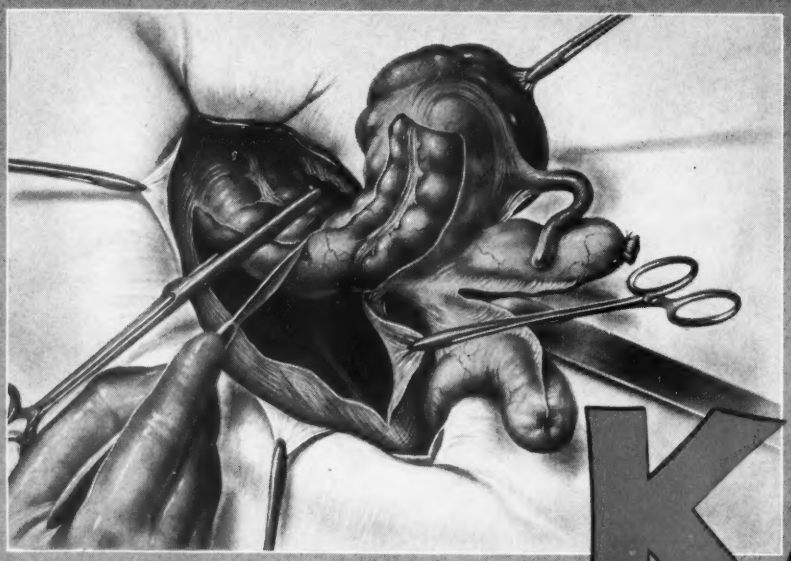

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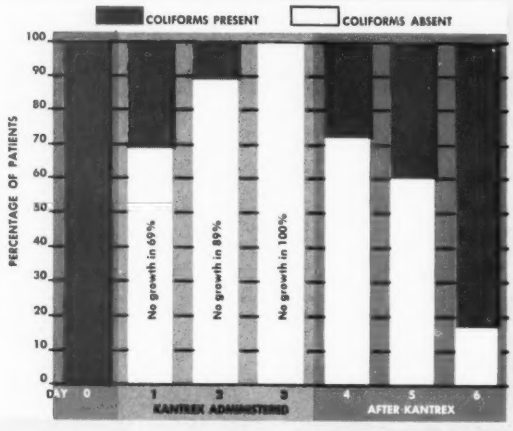
COLIFORMS REMOVED FROM STOOLS OF MAJORITY OF PATIENTS AFTER ONE DAY OF KANTREX THERAPY[1]



In this study, coliforms were found in all 18 control specimens before KANTREX was administered. By the end of the first day of therapy, they had been removed from 69% of the patients; by the end of the second day, from 89% of the patients; and by the end of the third day, from all of the patients. Following cessation of therapy, the intestinal microflora returned rapidly to normal. KANTREX dosage consisted of 1 Gm. (2 capsules) every hour for 4 hours, then 1 Gm. every 6 hours for 72 hours

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References: 1. Cohn, I., Jr.: Annals N. Y. Acad. Sci. 76:212, 1958. 2. Cohn, I., Jr., and Longacre, A. B.: S. G. & O. 108:100, 1959. 3. Finegold, S. M., *et al.*: Annals N. Y. Acad. Sci. 76:319, 1958.

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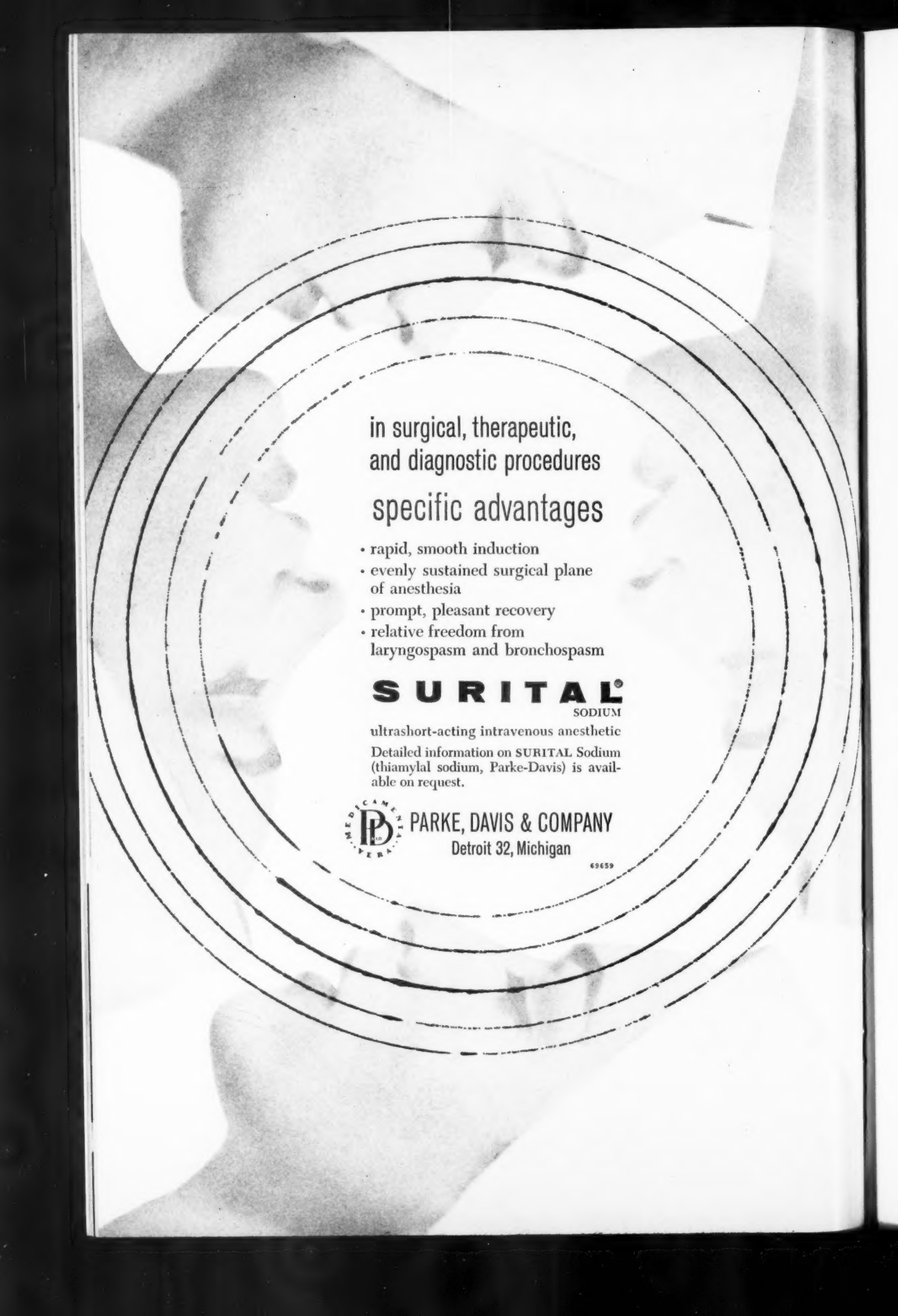
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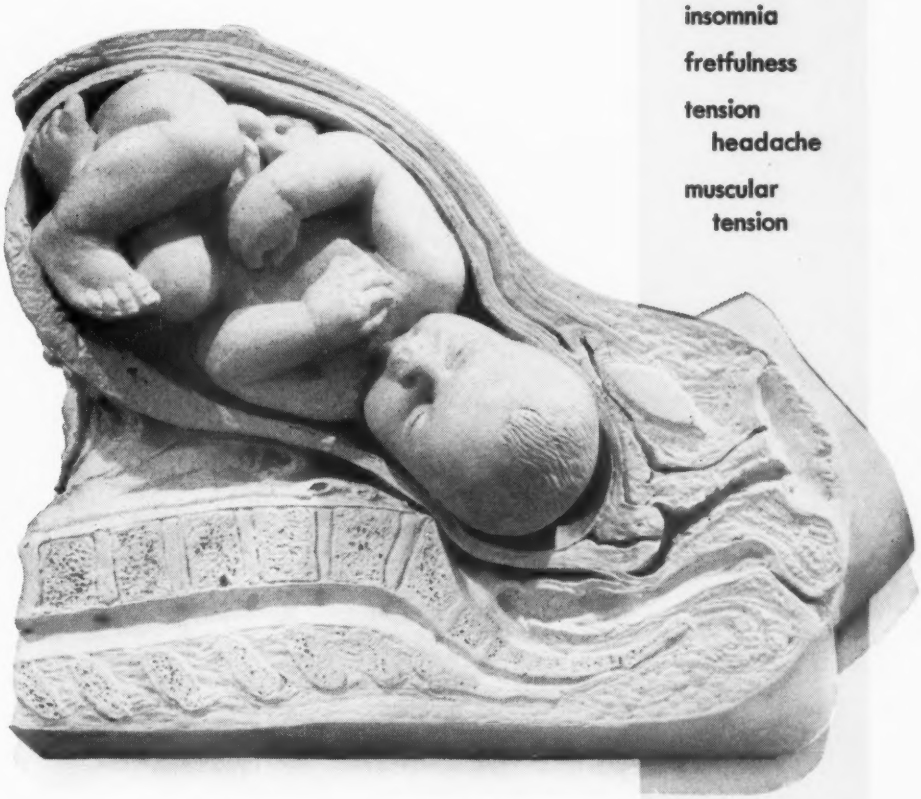

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1. English, A. R., and McBride, T. J.: Proc. Soc. Exper. Biol. & Med. 100:880 (Apr.) 1959. 2. Celmer, W. D.: Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959, p. 277. 3. English, A. R., and Fink, F. C.: Antibiotics & Chemother. 8:420 (Aug.) 1958.

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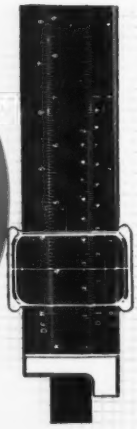

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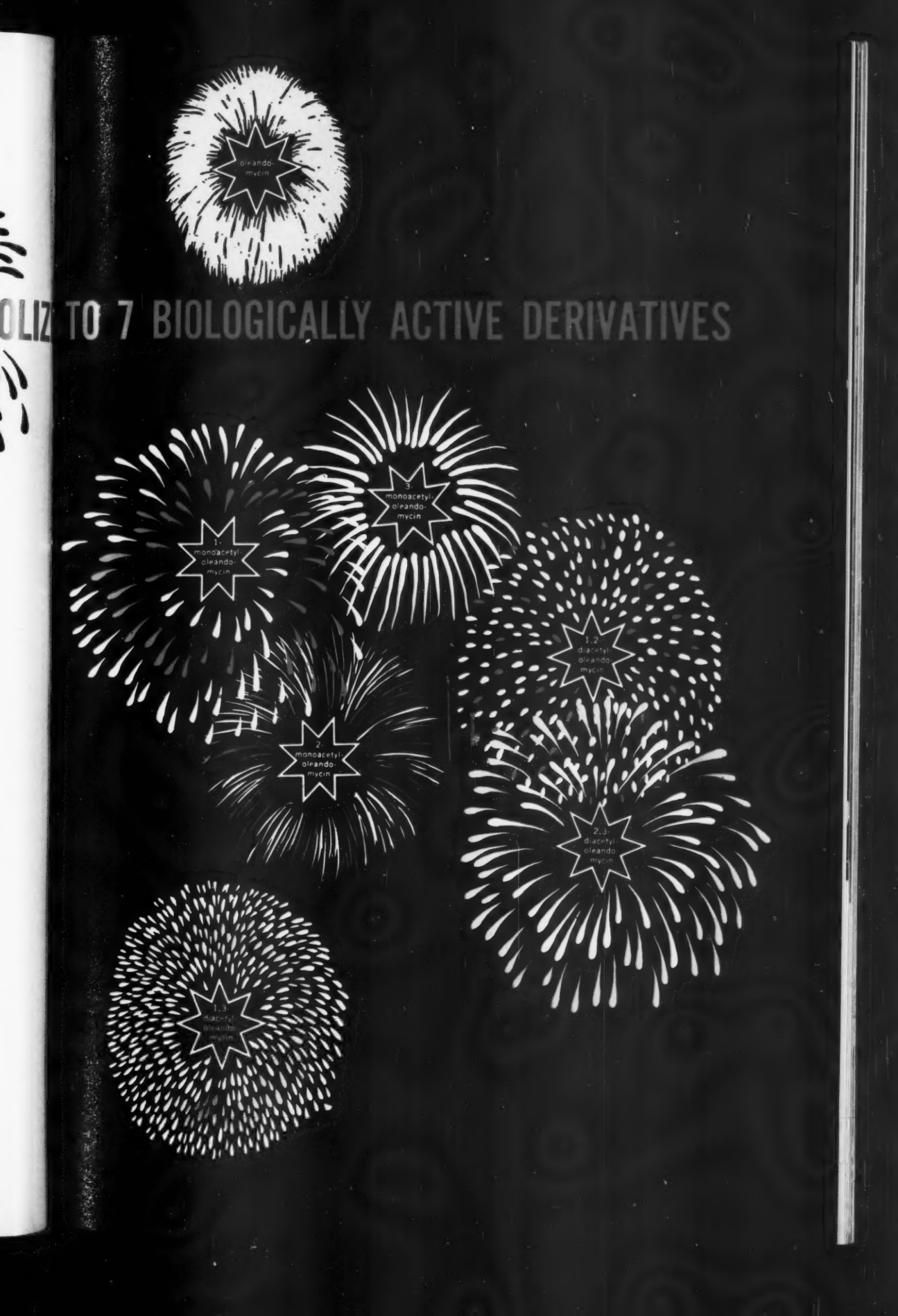
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References: 1. Cronk, G.A.; Naumann, D.E., and Casson, K.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia Inc., 1958, p. 397. 2. Childs, A.J.: Brit. M.J. 1:660 (Mar.) 1956. 3. Newcomer, V.D.; Wright, E.T., and Sternberg, T.H.: Antibiotics Annual 1954-1955, New York, Medical Encyclopedia Inc., 1955, p. 686. 4. Gimble, A.I.; Shea, J.G., and Katz, S.: Antibiotics Annual 1955-1956, New York, Medical Encyclopedia Inc., 1956, p. 676. 5. Stone, M.L., and Mersheimer, W.L.: Antibiotics Annual 1955-1956, New York, Medical Encyclopedia Inc., 1956, p. 862. 6. Campbell, E.A.; Prigot, A., and Dorsey, G.M.: Antibiotic Med. & Clin. Ther. 4:817 (Dec.) 1957.

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of left humerus with partial removal by curettement of a lesion in the marrow cavity.

Radiographs, preoperative and postoperative. Color photographs, showing essential steps in the surgery.

1. Incision at anterolateral aspect of the arm near insertion of the deltoid muscle.

(Turn page for additional illustrations)

Exploratory Fenestration (Continued)

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2. Small cortical window has been made in the humerus showing the underlying pathologic lesion.

3. Cortical window has been enlarged and the lesion in the marrow cavity partially curetted.

Note: Kodak Ektachrome roll film, used to make the illustrations for this picture sequence, may also be obtained for miniature cameras and sheet-film cameras.

4. Wound prior to closure. Two polyethylene tubes in place, one for suction, the other for insertion of antibiotics.

5. Technician preparing to radiograph patient in surgery to show extent of dissection in marrow cavity. Radiographs read wet, gave surgeon quick progress picture.

Postoperative radiograph made week following exploratory fenestration. Examination of resected tissue showed lesion to be a chondrosarcoma.

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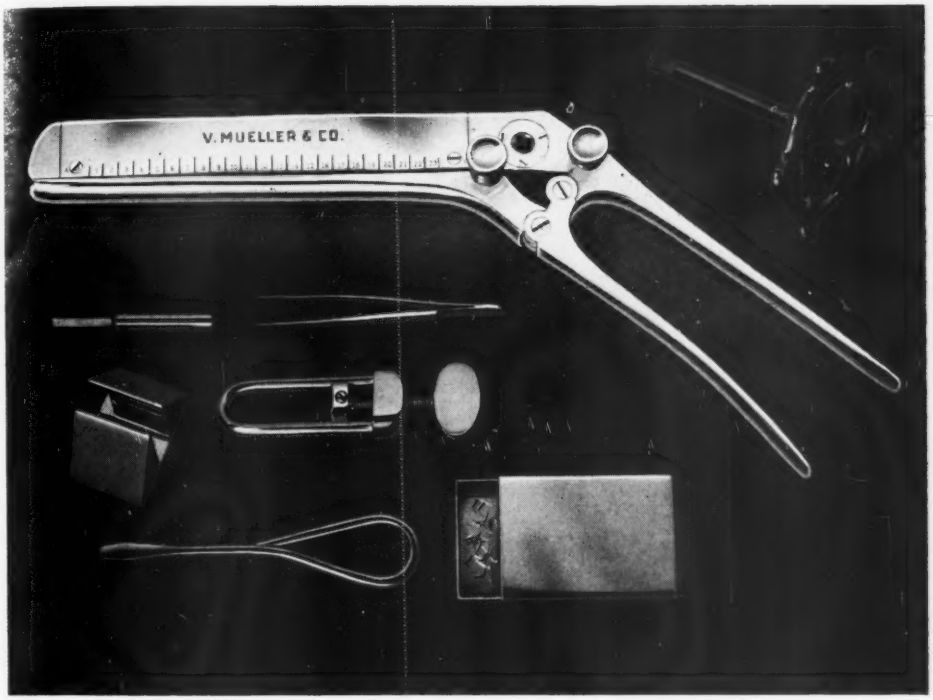

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1. Kareha, L. G., de Quevedo, N. G., Tighe, P., Kehrli, H. J., "Evaluation of Ilopan in Postoperative Abdominal Distention," Western J. Surg. Obs. & Gyn., 66:220, 1958.
2. Stone, M. L., Schlussel, S., Silberman, E., Mersheimer, W. L., "The Prophylaxis and Treatment of Postpartum and Postoperative Ileus with Pantothenyl Alcohol," Amer. J. Surgery, 97:191, 1959.

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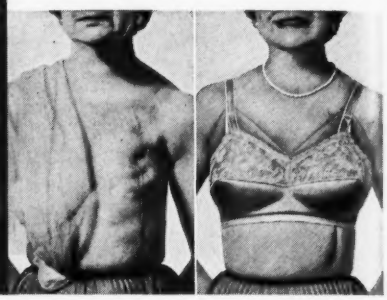

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* *Sklar T-C® Needle Holders incorporate Tungsten Carbide as an integral part of the jaws. This revolutionary development eliminates the disadvantages of welded inserts.*

T-C Jaws Assure...

POSITIVE GRIP... The hard surface of the jaws combined with very fine hand filed serrations prevents rotation with the important advantage of avoiding damage to fine suture needles.

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These superior, dependable instruments are priced slightly higher than our standard pattern Needle Holders.

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Pat. No. 2,795,225

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Acetophenetidin ..... gr. 2½
Acetylsalicylic Acid .... gr. 3½
Caffeine ..... gr. ½

'TABLOID'
'EMPIRIN' COMPOUND® WITH CODEINE PHOSPHATE*

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Caffeine ..... gr. ½
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No. 3
Acetophenetidin ..... gr. 2½
Acetylsalicylic Acid .... gr. 3½
Caffeine ..... gr. ½
Codeine Phosphate .... gr. ½

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Caffeine ..... gr. ½
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*Subject to Federal Narcotic Regulations

...providing the desired gradation of potencies for relief of varying intensities of pain

IN
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myalgias
common cold
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minor trauma
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migraine
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fractures
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relief of pain of all degrees of severity up to that which requires morphine

AND IN
fevers
dry, unproductive coughs

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...reduces appetite'...elevates mood...eases tensions of dieting...*without* overstimulation, insomnia, or barbiturate hangover.

anorectic-ataractic

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- in mixed vaginal infections
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- in postpartum care
- after vaginal surgery

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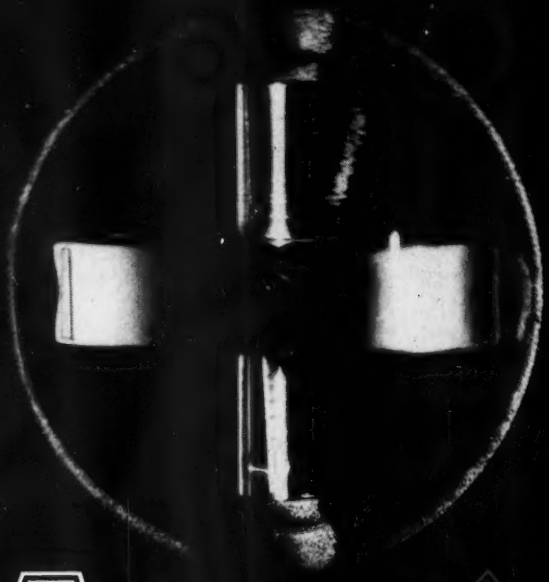
minimal disturbance
of the patient's chemical and psychic balance...



still unsurpassed for total corticosteroid benefits

Arist

Substantiated by published reports of leading clinicians:

- **effective control** of allergic and inflammatory symptoms[1-20]
- **minimal disturbance** of the patient's chemical and psychic balance[1-3,5,6,19]

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Triamcinolone LEDERLE

At anti-inflammatory and antiallergic levels ARISTOCORT means:

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- **euphoria and depression rare**
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- **low incidence of peptic ulcer**
- **low incidence of osteoporosis with compression fracture**

Indications: rheumatoid arthritis; arthritis; respiratory allergies; allergic and inflammatory dermatoses; disseminated lupus erythematosus; nephrotic syndrome; lymphomas and leukemias.

Precautions: With ARISTOCORT all traditional precautions to corticosteroid therapy should be observed. Dosage should always be carefully adjusted to the smallest amount which will suppress symptoms. After patients have been on steroids for prolonged periods, discontinuance must be carried out gradually.

Supplied: Scored tablets of 1 mg. (yellow); 2 mg. (pink); 4 mg. (white); 16 mg. (white).

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List of References 1-20 supplied on request.

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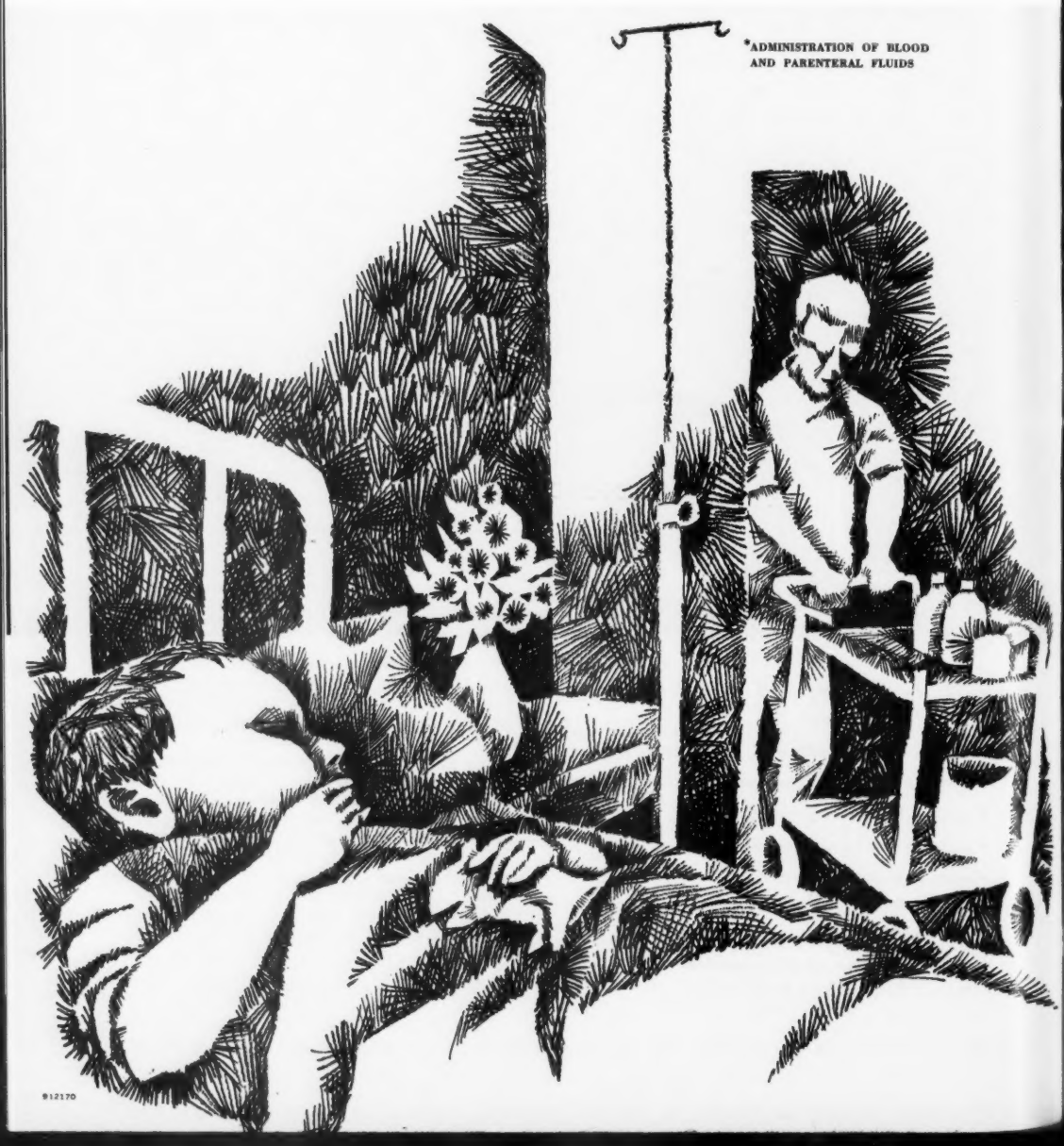

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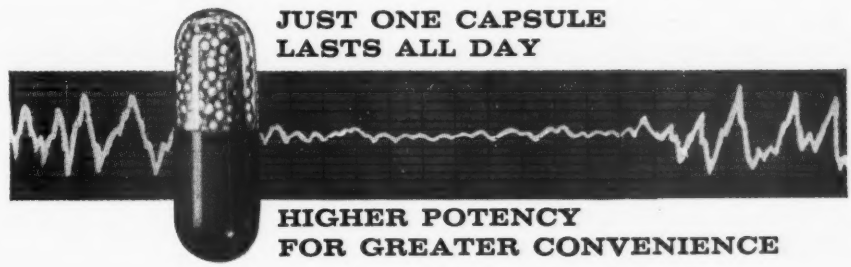

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- relieves *both* mental and muscular tension without causing depression
- does not impair mental efficiency, motor control, or normal behavior

Usual dosage: One capsule at breakfast, one capsule with evening meal

Available: *Meprospan-400*, each blue capsule contains 400 mg. Miltown (meprobamate)
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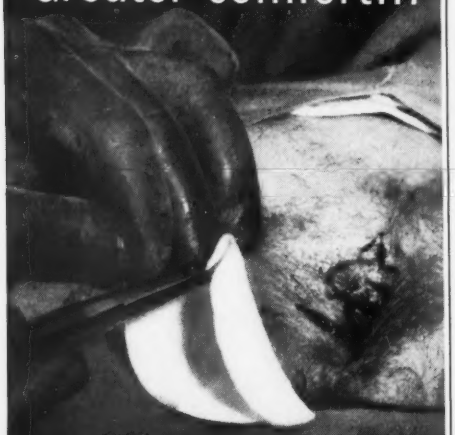

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Postsurgical patients appreciate the extra comfort, the "extra attention" of *TUCKS:*

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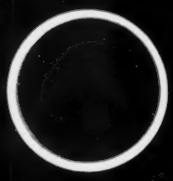
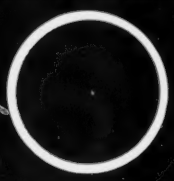


increases accelerator globulin

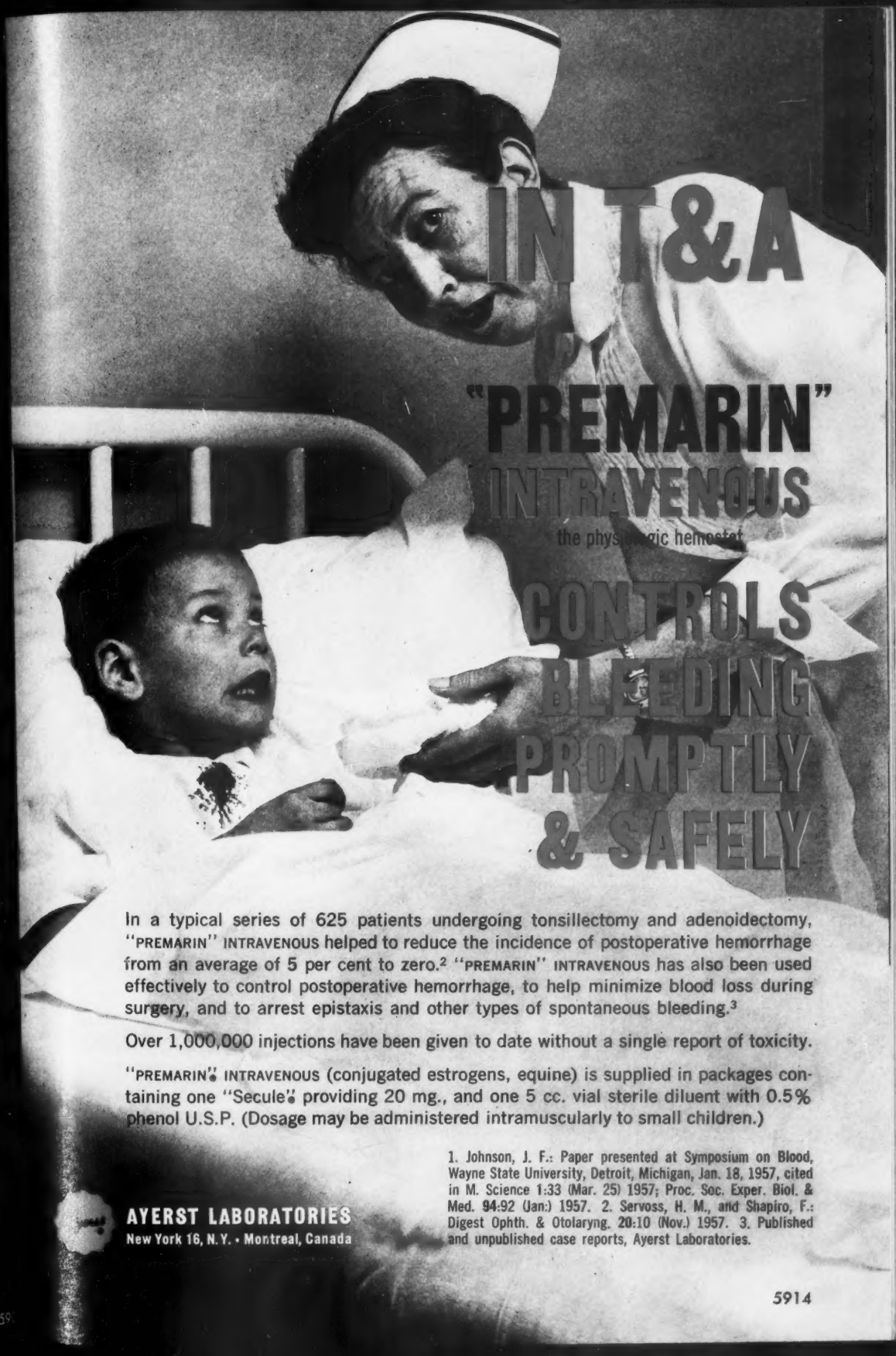
and simultaneously depresses antithrombin activity



within 15 to 30 minutes.

Thus, **coagulation** is **enhanced**

to achieve prompt hemostasis.



In a typical series of 625 patients undergoing tonsillectomy and adenoidectomy, "PREMARIN" INTRAVENOUS helped to reduce the incidence of postoperative hemorrhage from an average of 5 per cent to zero.[2] "PREMARIN" INTRAVENOUS has also been used effectively to control postoperative hemorrhage, to help minimize blood loss during surgery, and to arrest epistaxis and other types of spontaneous bleeding.[3]

Over 1,000,000 injections have been given to date without a single report of toxicity.

"PREMARIN" INTRAVENOUS (conjugated estrogens, equine) is supplied in packages containing one "Secule" providing 20 mg., and one 5 cc. vial sterile diluent with 0.5% phenol U.S.P. (Dosage may be administered intramuscularly to small children.)

1. Johnson, J. F.: Paper presented at Symposium on Blood, Wayne State University, Detroit, Michigan, Jan. 18, 1957, cited in M. Science 1:33 (Mar. 25) 1957; Proc. Soc. Exper. Biol. & Med. 94:92 (Jan.) 1957. 2. Servoss, H. M., and Shapiro, F.: Digest Ophth. & Otolaryng. 20:10 (Nov.) 1957. 3. Published and unpublished case reports, Ayerst Laboratories.

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Highly effective in the management of a wide variety of dermatological disorders.

Typical cases treated

Sex	Age	Diagnosis
F	5	tinea capitis
M	5	tinea corporis
M	45	furunculosis
F	42	recurrent furunculosis
M	30	sebaceous cyst
M	2½	seborrheic dermatitis
M	16	acne vulgaris
F	33	abscess
F	21	infected dermatitis
M	39	bacterial folliculitus
M	19	impetigo
F	48	moniliasis
M	33	secondary impetigo
M	18	infected comedone
F	52	monilial paronychia
M	48	localized neurodermatitis
M	44	kerion
M	3 months	herpes simplex
M	30	multiple folliculitis
F	19	acne
M	26	infected abrasion
M	9	palmar infection
F	43	recurrent folliculitis
M	38	epidermatophytosis
M	27	infected sebaceous cyst
M	18	acne conglobata
F	40	suppurative paronychia
M	32	multiple abscesses
M	23	tinea pedis

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depresses appetite and elevates mood

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eases tensions of dieting
(yet without overstimulation, insomnia or barbiturate hangover)

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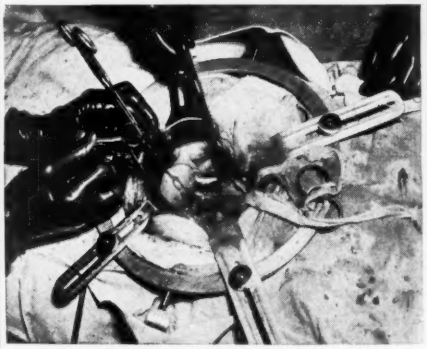

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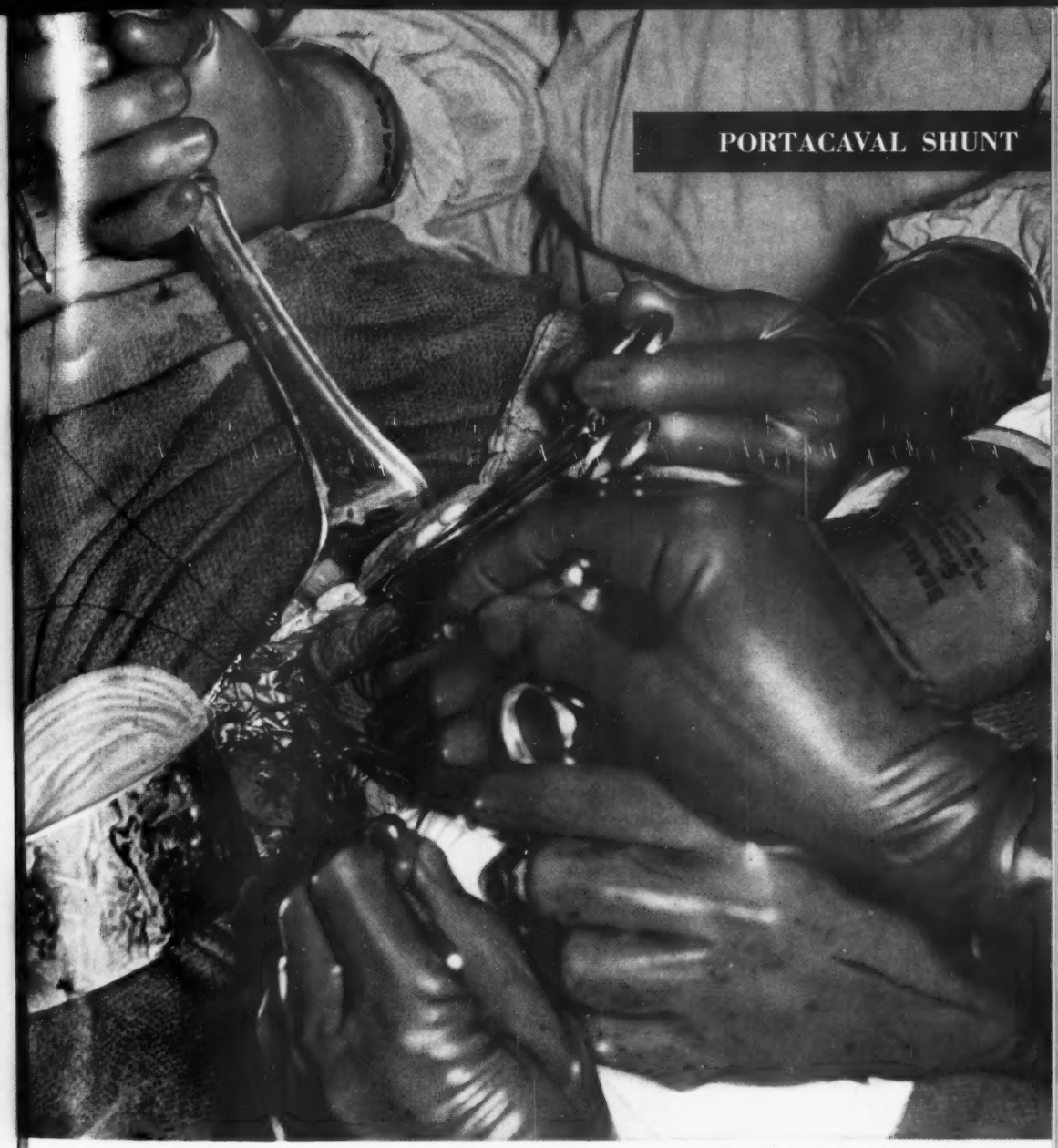

No. 6 of an operative series—for details, see next page

Approach the Critical Step Confidently in

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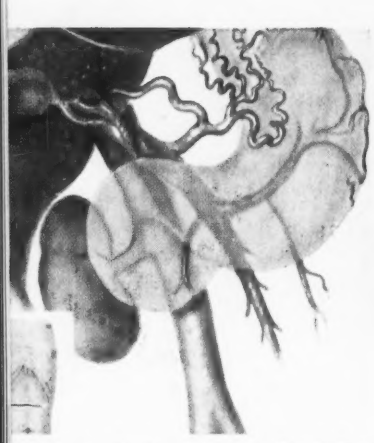
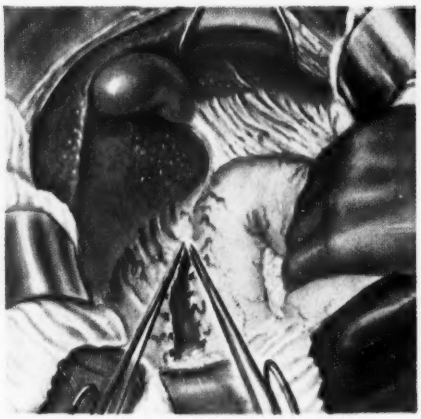
Deep in an incision, the maximum tactile sensitivity of Brown Milled Surgeons' Gloves by Seamless assures unmatched "sightless seeing." Minimal radial bind across knuckles and palm guarantees maximum comfort. And especially important to many surgeons, their hypoallergenic property eliminates the possibility of latex dermatitis.

KEY ADVANCES IN OPERATIVE TECHNICS*

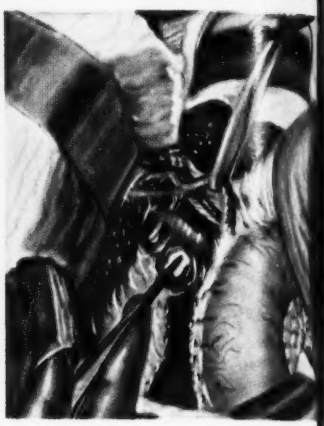
Portacaval Shunt[1]



1. In cirrhosis, splanchnic blood flow by-passes the liver in an extensive network of hepatofugal collaterals. Note large portocoronary anastomosis. Portacaval shunt, indicated when ascites and esophogeal varices occur, directs portal blood into the vena cava, lowering portal tension. To determine operability, abdomen is first entered with a transverse incision. (See inset.)



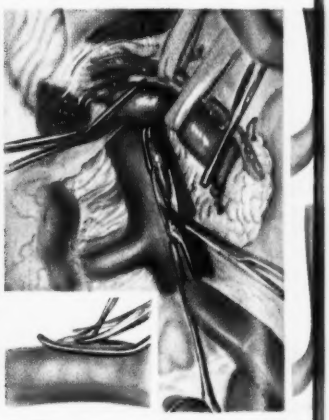
2. Abdominal incision is continued into 8th or 9th intercostal space and through the diaphragm. This permits upward displacement of an enlarged liver. The colon and small intestines are retracted. The descending duodenum is mobilized. In contrast to normal, its right border is the site of a rich network of collateral veins and venules which must be carefully secured and ligated.



3. The hepatic artery and common bile duct are identified and the latter mobilized from duodenum to bifurcation. A Penrose drain is passed around the duct to utilize for traction as necessary. Vigilantly clamping and ligating the many large venous collaterals, the portal vein is gradually exposed by gentle dissection with spreading clamps, scissors, and tiny sponge-clamp "wiping."

4. A maximum length of untraumatized portal vein must be mobilized. This involves freeing it from its exit behind the pancreas to its bifurcation at the porta hepatis. When the coronary vein branches off the portal vein it should be ligated by transfixion flush with the portal wall. (See inset.) Smaller branches are also transfixed and ligated with the portal vein. The portocoronary collateral shown behind the portal is ligated.

5. The inferior vena cava is exposed from under the surface of the liver to just below the renal vein. Only the anterior two-thirds should be dissected free in order to avoid injuring the lumbar branches. The portal vein is then clamped just superior to the head of the pancreas. The upper end of the vein is then quickly ligated immediately below the bifurcation and reinforced with a transfixion suture.



6. The upper end of the portal vein is divided, then irrigated with heparin solution. The caval clamp is placed on the antero-mesial surface. No tension on the anastomosis is permitted. To avoid too large a caval opening only half the ellipse is cut with the first bite of the curved scissors. Once the second bite is completed (a), two angle sutures are placed (b); these are then tied to running sutures uniting the walls of the vessels.

Portacaval Shunt is one of a series of surgical drawings illustrating important new operations perfected during the past decade. It is brought to you as a service by Seamless, the world's largest manufacturer of surgeons' gloves. If you would like to examine the Brown Milled Surgeons' Glove by Seamless, write for a sample giving your glove size.

*Based on an opinion survey of 2,500 general surgeons.

1. Rousselot, L. M.: Bleeding Esophageal Varices. Portal Hypertension by Liebowitz, H. R., Springfield, Ill., Charles C. Thomas, 1959.

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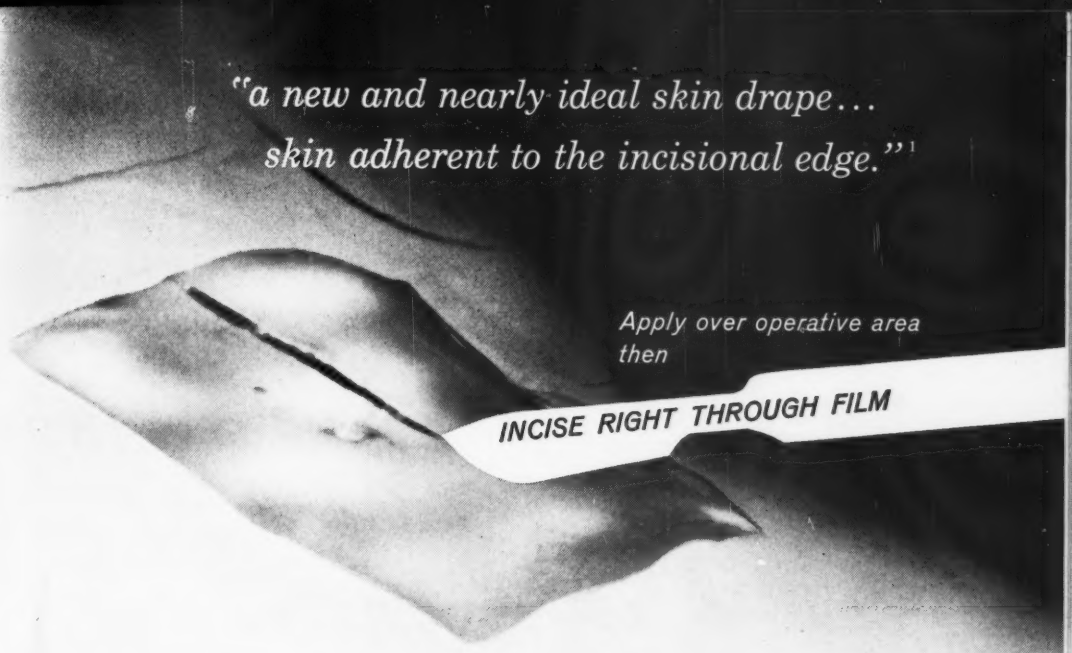
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Patents Pending

1. Adams, Ralph, M. D. : Med. Times, 86:1119-1127 (Sept.) 1958.

Initial clinical studies on Vi-DRAPE Film were conducted by Carl Walter, M.D., Peter Bent Brigham Hospital, Boston.

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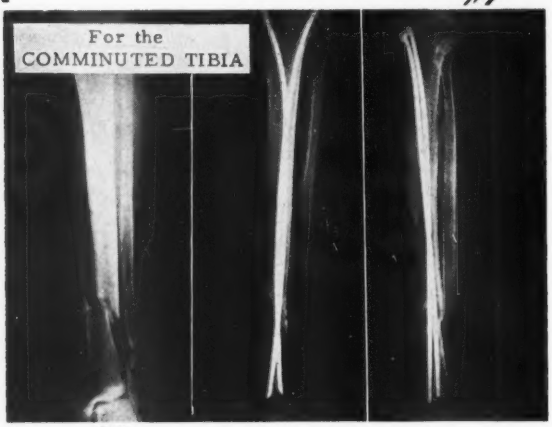

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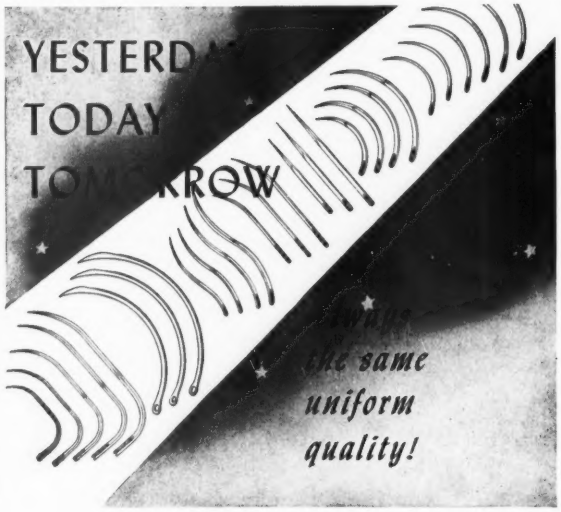

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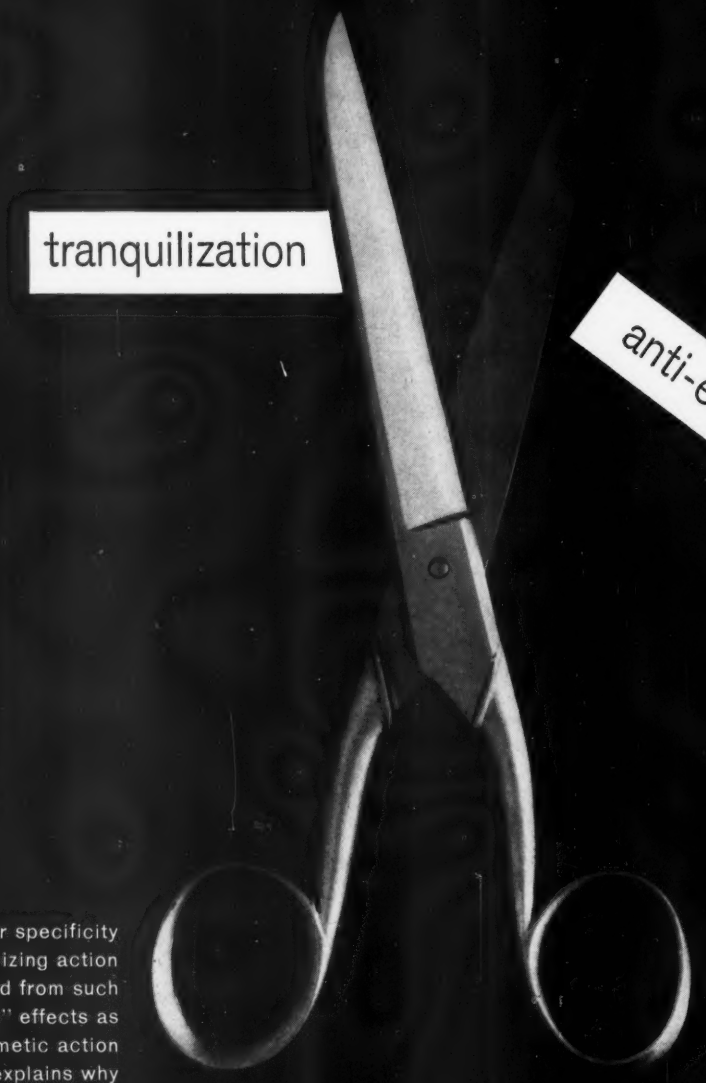

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of tranquilizing action
—divorced from such
"diffuse" effects as
anti-emetic action
—explains why

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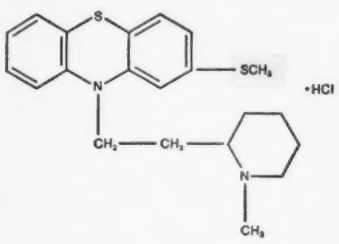
ne advance in tranquilization:
rea r specificity of tranquilizing action results in fewer side effects



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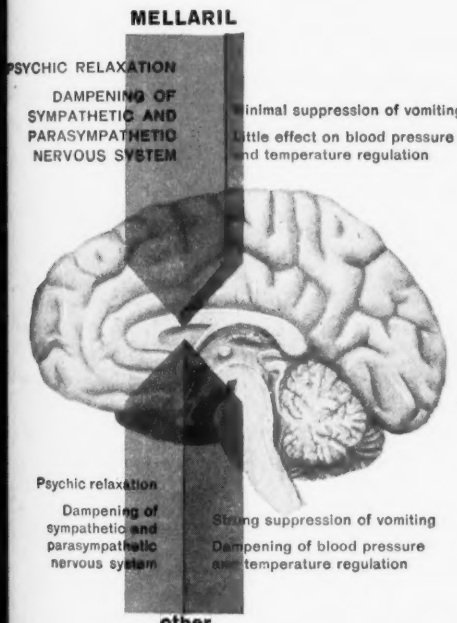
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DAMPENING OF SYMPATHETIC AND PARASYMPATHETIC NERVOUS SYSTEM
Minimal suppression of vomiting
Little effect on blood pressure and temperature regulation
Psychic relaxation
Dampening of sympathetic and parasympathetic nervous system
Strong suppression of vomiting
Dampening of blood pressure and temperature regulation
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3 **A notable absence of extrapyramidal stimulation.**

4 **Lack of impairment of patient's normal drive and energy.**

5 **Virtual freedom from such toxic effects as jaundice, photosensitivity, skin eruptions, blood forming disorders.**

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MODERATE—where agitation exists in psychoneuroses, alcoholism, intractable pain, senility, etc.	25 mg. t.i.d.	50-200 mg.
SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.:		
Ambulatory	100 mg. t.i.d.	200-400 mg.
Hospitalized	100 mg. t.i.d.	200-800 mg.
CHILDREN: BEHAVIOR PROBLEMS IN CHILDREN	10 mg. t.i.d.	20-40 mg.

ELLARIL Tablets, 10 mg., 25 mg., 100 mg.

tfeld, A. M. Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959.

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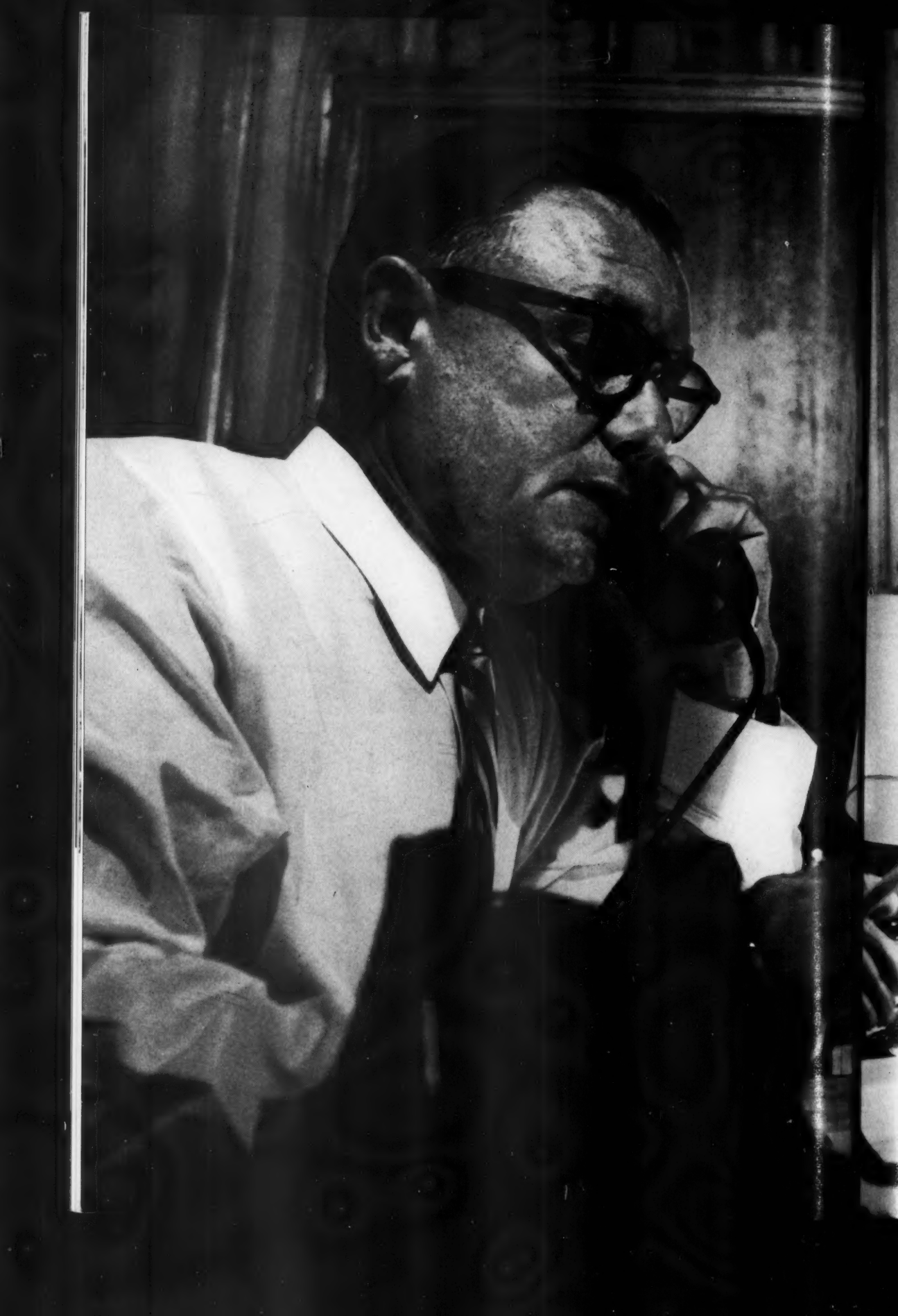

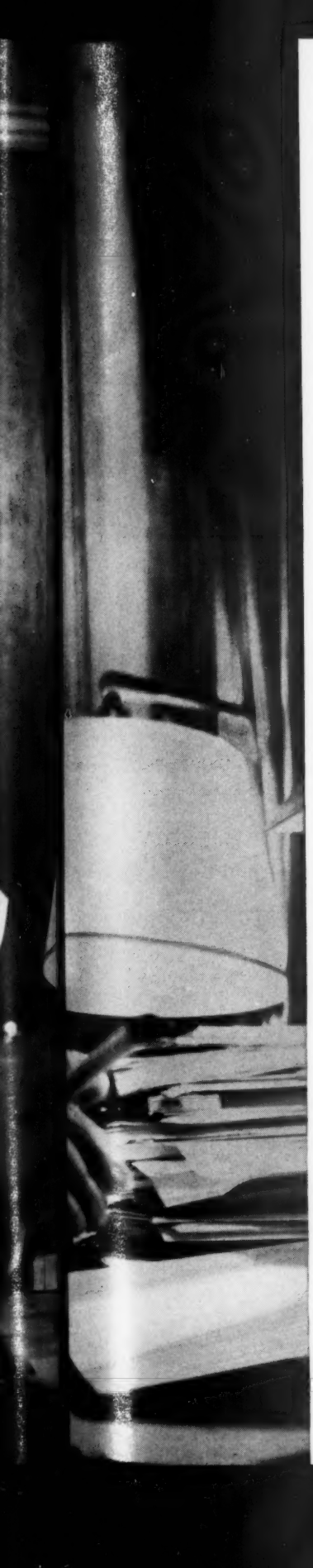

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The man on the 'phone is Terry Vardaman. Maybe you know him. The chances are good that you do if you're a physician in or around Birmingham, Alabama. Hunter, fisherman, flower hobbyist, and Wyeth Territory Manager, Vardaman has been on the job there for most of his working life.

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*Bonica, J.J.: J.A.M.A. 168:734 (Oct. 11) 1958.

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Krantz, J. C., Jr.: The restless patient—A psychologic and pharmacologic viewpoint. Current M. Digest *25*:68, Feb. 1958.

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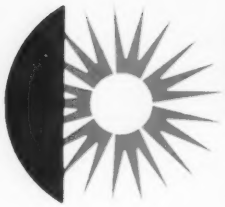

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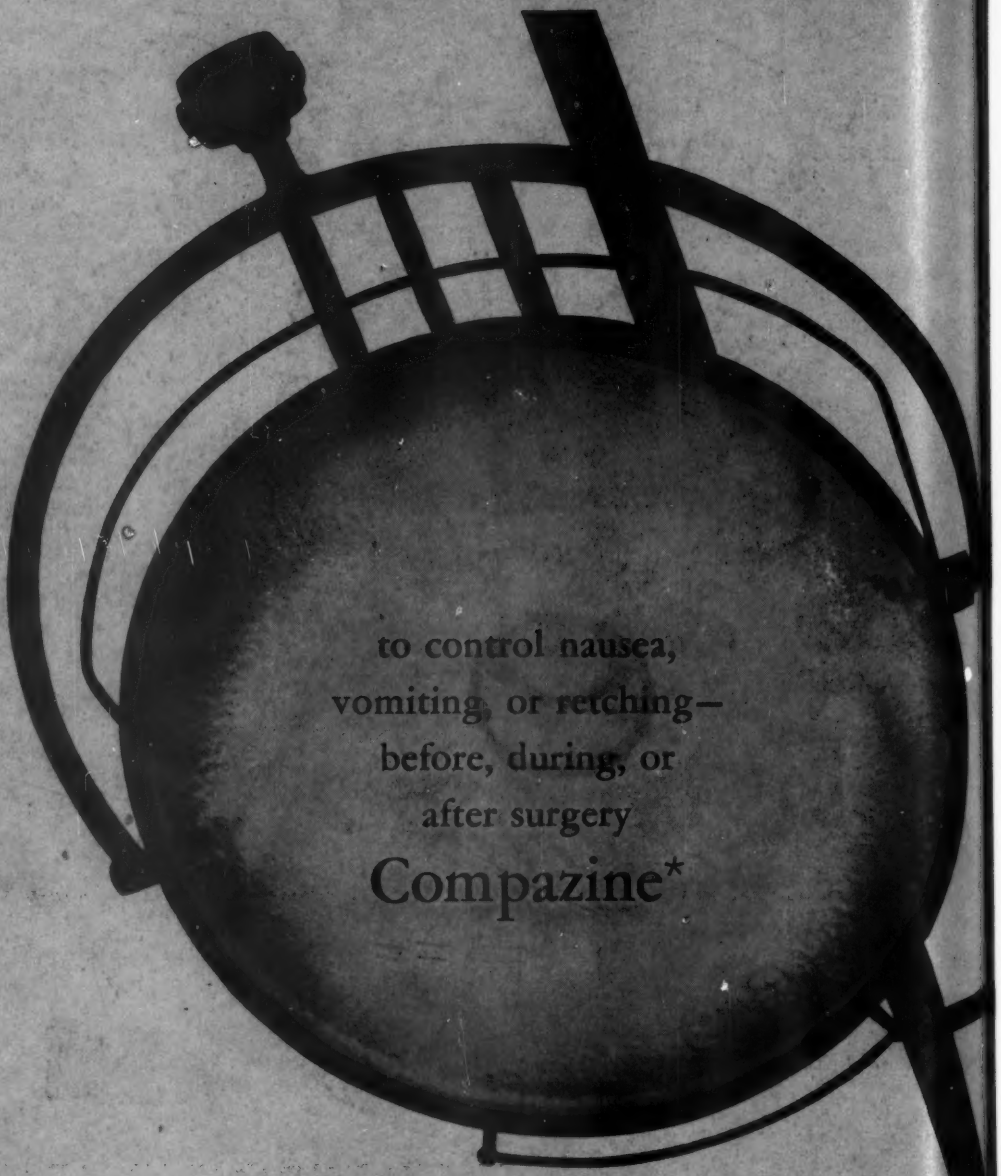

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